Chapter 8: Chromosomes and Chromosomal Anomalies

Introduction and an Historical Curiosity

The word chromosome is derived from the Greek words *chromos*, meaning color, and *soma*, meaning body. They were discovered in the latter half 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, who to the best of our knowledge never even saw a chromosome!

The Karyotype

Over the past century, the technology for staining chromosomes and viewing them under a microscope has dramatically improved and has led to the development of a subfield of genetics called *cytogenetics*—the study of chromosomes and chromosomal aberrations. This science begins with the construction of a *karyotype* which is literally a picture of stained chromosomes. Construction of a typical karyotype begins with living

tissue, usually a particular type of white blood cell called *lymphocytes*[1] obtained from a

blood sample. The lymphocytes are kept alive and dividing in a culture and then, in a

series of complicated steps[2], are stained and examined under a 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 the need for the tedious photographic

and cut and paste steps. An example of a karyotype is given in Figure 8.1.

   [Insert Figure 8.1 about here]

        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.

The Nomenclature of Chromosomes

        There is a standard terminology[3] 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

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[1] Lymphocytes are actually colorless cells formed in the lymph nodes, spleen, and a few other organs. The two major types of lymphocytes, B cells and T cells, play an important role in the immune response.
[2] The cells are kept in a culture that promotes cell division. After 48 to 72 hours, chemicals like colchicine or colcemid are added to arrest cell division at a crucial stage of cell division (prophase or metaphase) when the chromosomes are especially condensed. The cells are placed onto a slide, and a low salt (hypotonic) solution is added to swell and eventually rupture the cells. They are then stained and photographed.
[3] The ISCN or International System for Human Cytogenetic Nomenclature.

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 8.2 provides a schematic for the banding pattern of chromosome 18. The

short arm, always 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 8.2, are derived from cells where the

chromosome is more elongated.[4] As the process of cell division progresses, the

chromosomes become more compacted and dense, leading to the banding pattern on the

left hand chromosome in Figure 8.2.[5]

   [Figure 8.2 about here]

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 25,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

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[4] Here, cells are in the prophase stage of cell division.

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.

Bands are denoted by the chromosome number, arm, and band number(s). 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.[6]

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.

Chromosomal Aberrations

Because chromosomal anomalies involve inheritance of extra genetic material or the

deletion of important genetic material, the vast majority of them are lethal and result in

spontaneous abortion. Nevertheless, conceptions that involve chromosomal anomalies are

surprisingly common. About 15% of all recognized pregnancies terminate in a

spontaneous abortion and over half of these involve identifiable chromosomal

abnormalities. The percentage of aberrations in unrecognized pregnancies (i.e., those

involving spontaneous abortion before pregnancy testing) is thought to be even higher.

Clearly, chromosomal aberrations encountered at or shortly after birth represent the tip of

an iceberg from the perspective of all human conceptions.

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[5] Denser banding comes from chromosomes in the metaphase stage.
[6] See Chapter 4 on parental imprinting.

Three chromosomal aberrations are very illustrative for behavioral purposes. We discuss them now.

The Down Syndrome

Down's syndrome involves inheritance of extra chromosomal 21 material. There are three forms of the Down syndrome. The most common form, accounting for over 95% of cases, is trisomy 21 or the inheritance of a whole extra copy of chromosome 21. The trisomy is an accident of birth and comes from the fact that one of the gametes—the sperm or the egg, but usually the egg—accidentally gets two copies of chromosome 21 instead of one[7]. Hence, this form of Down's, like the overwhelming number of chromosomal abnormalities, does not run in families. The second most common form comes from translocation, a phenomenon that occurs when a chromosome breaks and then one of the fragments becomes attached to another chromosome. In Down's, a section of chromosome 21 breaks and attaches itself to another chromosome, often chromosome 14. The Down's child will then inherit that chromosome with the extra piece of 21. The least common form is mosaicism, accounting for about 1% of cases. Here, some of the person's cells carry the normal chromosome complement while others carry extra chromosome 21 material. The extent of medical and psychological problems in a mosaic depends upon the percentage of cells with the extra genes from chromosome 21.

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[7] This is called nondisjunction—the phenomenon whereby a pair of chromosomes fails to segregate, each into its own gamete.

The critical region on chromosome 21 that results in the Down syndrome is thought to be on the long arm (i.e., *q* arm), specifically band 22. Considerable research is now being conducted to narrow this region and locate the gene(s) responsible for the disorder.

About 1 in 600 to 700 births has Down's syndrome, although the prevalence among pregnancies is much higher. A large number of physical features are associated with Down's. They include flattening of the nasal bridge; epicanthal folds that give the eyes an Asian appearance[8]; protruding tongue; small ears; simian crease (the "lifeline" on the palm of the hand extends all the way across the palm); unusual fingerprints and toeprints (a.k.a. *dermatoglyphics*); and short stature. It is crucially important to recognize that few Down's people exhibit all the physical aberrations and no single physical characteristic is present in all Down's cases. Affected individuals are at high risk for heart defects, leukemia, and problems with immune functioning. Their brains also show the typical pathology of Alzheimer's disease,[9] a fact which led researchers to concentrate on chromosome 21 in their search for Alzheimer's genes. Males are invariably infertile, but there have been cases of females bearing children. Because medical technology can relieve many of the medical complications, people with Down's can now live into their 50s and 60s, while in the 1930s, most died before their 10th birthday.

The major risk factor for having a Down's child is maternal age. Women pregnant in their teens and early twenties have a risk for a Down's child of roughly 1 per 1,000 to

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[8] In earlier times, the term Mongolism was used to describe Down's because of the appearance of the eyes.

2,000 births. Risk increases gradually so that by the early thirties it is about 1 in 750.

Thereafter, there is a marked increase so that by age 45 the risk is almost 1 in 15 births.

Many obstetricians now counsel clients who are having children later in life about the risk

for a Down's child. And like many issues of reproductive choice, there are sharp

differences in opinion among prospective parents. Those not wishing to bear a Down's

child usually elect to have amniocentesis or chorion villus sampling performed early in the

pregnancy[10] and, if the results are positive, choose to abort the fetus. As a result of

elective abortion, the prevalence of Down's syndrome has probably decreased.

With few exceptions, Down's cases have mental retardation and learning

disabilities. On average, the degree of mental retardation is moderate, but the extent of

cognitive impairment is remarkably variable. A few Down's cases may require

institutionalization while others can be mainstreamed in schools. With specialized

education and training, a significant proportion of Down's cases would actually be able to

hold jobs. They might not be the neurosurgeons or appellate judges of our society, but

they, like a large number of people with mental retardation, could function well in

stocking shelves, cleaning up stores after hours, and running errands. The fact that few

actually work in such enterprises says more about our society's willingness to train and

employ these people than it does about their cognitive capabilities.

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[9] Neurofibulary tangles (i.e., the neurofibers that assist in transporting molecules from the cell body to the dendrites become tangled) and plaques (small, disk-shaped formations in the neurons).

[10] Usually performed between week 15 and 17 of pregnancy, amniocentesis involves the insertion of a needle into the sac surrounding the fetus and extraction of a fluid sample (a.k.a. amniotic fluid and amniotic sac). A karyotype is then done on the fetal cells harvested from the fluid. Chorion villus sampling is quite similar but involves a biopsy of the developing placenta and can be performed earlier than amniocentesis, usually between week 9 and 12 of pregnancy.

Another characteristic of Down's is delayed development. The Down's child often takes 3 to 24 months longer than a normal child to walk.

Down's cases are real human beings. Yes, they have differences from us folks with 46 chromosomes, but they laugh, socialize, and love affection just like us. You and I have acquaintances with rough edges who can be disruptive and overbearing at times. So too can some individuals with Down's. But you and I also know sweet, disarming people whose pleasantness so impresses us that we silently wonder to ourselves why we cannot be more like that person. You and I will also encounter such people among those with the Down syndrome.

The largest lesson for the behavioral scientist is in the variability of Down's cases. This is a lesson that will be reinforced time and time again as we examine genetic disorders. The inheritance of a whole extra chromosome 21 can result in a wide range of intellectual abilities, developmental potential, and personality.

Turner's Syndrome

Turner's syndrome (TS) involves loss of X chromosomal material in a person with another X chromosome. The most common karyotype, accounting for slightly over half the cases, is 45,X (also written as 45,XO) signifying that an entire sex chromosome is missing. Individuals with only part of an X chromosome, those with certain structural alteration in an X, and mosaics make up the remaining cases. Although the prevalence of TS is about 1 in 2,500 to 5,000 births, it is the largest detectable chromosomal abnormality among spontaneous abortions. Some authors estimate that over 99% of

Turner conceptions fail to make it to term. About 80% of the Turner's cases with a

45,XO karyotype fail to inherit a chromosome from their fathers.

All Turner's people are phenotypic females.[11] Physically, almost all Turner's

women have short stature. Otherwise, the physical characteristics of many Turner's are

so subtle and blend so well into the normal range that they are indistinguishable to anyone

but an experienced professional. These characteristics include obesity (often mild),

puffiness[12] of the hands and feet, unusual shape and positioning of the ears, a broad chest

with widely spaced nipples, and a thick, webbed neck.

Like all chromosomal anomalies, Turner's women are at risk for a variety of

medical complications. The most notable of these is irregular development of the

ovaries.[13] As a result, the Turner's girl fails to develop secondary sex characteristics

(menstruation, breast development, and pubic hair) and, with rare exception, are infertile.

Indeed, a significant proportion of cases first came to medical attention because of

concern over the absence of maturation in the teenage years. Thankfully, TS can be

treated with hormone replacement therapy to promote adolescent growth and the

development of secondary sex characteristics. Infertility, however, is rarely ameliorated.

Behaviorally, the most notable feature of TS is normality. Despite the absence of

a whole chromosome, the detectable differences between TS and controls are small

relative to the overlap between the two groups. Cognitively, TS have notably lower

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[11] The natural course of sex development in humans is female. It takes the presence of a Y chromosome to masculinize a developing fetus.
[12] Lymphedema.
[13] Gonadal dysgenesis.

means than controls on spatial-perceptual tasks (e.g., the ability to mentally rotate a three dimensional image) and slightly lower averages on quantitative skills. Verbal intelligence is normal, and indeed there have been reports that women with TS may actually have higher than average vocabulary and reading skills.

Many early clinical descriptions of TS portray the women as having stereotypically feminine interest patterns. As children they preferred frilly dresses to jeans and enjoyed playing with dolls more than climbing trees. However, no systematic data were gathered on this issue and it would be unwise to generalize these clinical impressions to the present day when gender roles have changed.

One of the most interesting findings about TS is that it has a small positive effect on emotional stability. TS women have slightly lower scores than normal women on personality measures of neuroticism, emotional stability, and stress reaction. This means that they are less likely to get upset after a stressful event, have more equable mood swings, and suffer less from tension and anxiety than their normal counterparts. The mean difference, however, is very small. There is considerably more overlap between the distributions of TS and normal women than there are mean differences.

The intriguing feature of TS is why it happens in the first place. In the discussion of Lyonization, we learned that all women are mosaics. One X chromosome is inactivated in every cell of the body. In TS, the single X chromosome is active in every cell. Why then should TS women be any different from women with two Xs? At present there is

no good answer to this question, but it may help to explain the surprising normality of TS

women.

XYY Syndrome

In the propagation of a sperm, nondisjunction may occur so that one gamete

inherits two Y chromosomes while the other gamete inherits no sex chromosomes. If the

gamete with no sex chromosomes fertilizes an egg, the resulting zygote will be inviable

and will die *in utero* (i.e., within the mother's womb). The gamete with the two Y

chromosomes, however, may actually fertilize the egg and produce a viable offspring.

The resulting zygote will have the XYY syndrome.

The most striking feature of the XYY syndrome—as indeed is characteristic of

most chromosomal anomalies involving the sex chromosomes—is the overwhelming

normality of the phenotype. Because XYY individuals have a Y chromosome, they are

always males. As a group, they tend to be tall and have several ill-defined learning

disabilities as children, but in most other regards would pass as completely normal

individuals throughout life. Their faces are not bizarre (as in Down's syndrome), they are

not mentally retarded (as in most cases of Fragile X), they do not have peculiar smelling

urine (as in phenylketonuria), and they do not have characteristic medical complications.

From a scientific viewpoint, the XYY genotype is remarkable more because of its

history in the sociology of science rather than because of any physical or psychological

deficits suffered by the individuals with this genotype. In the 1960's, several researchers

reported an increased frequency of XYY individuals in institutional populations,

particularly in legally incarcerated populations (i.e., prisons or institutions for psychiatric

patients who committed crimes.) A flurry of speculation followed these empirical

reports suggesting, either overtly or between the lines, that the inheritance of an extra Y

chromosome "over masculinized" XYY individuals and led to a heightening of sex and

gender stereotypical behavior. In the extreme, the XYY male was characterized as being

something of a hypermasculinized sexual psychopath particularly prone to violence and

rape.

More sober minds of that era—including several of the researchers who reported

the initial association between XYY and institutionalization—recognized that prospective

longitudinal designs were required to fully characterize the syndrome. Studies of

institutional populations fail to sample those XYY males who develop normally. Only

the identification of XYY males at birth and longitudinal study of these individuals could

resolve the issue.

A Harvard researcher, XXX, proposed such a study in 19XX. However, there

was a strong backlash to this type of study from other scientists. Fearing that identifying

these boys at birth and labeling them as antisocial might create a self-fulfilling prophecy, a

group of researchers effectively stopped such research in its tracks.

This controversy, however, influenced research in the USA but left the question

open for scientists in other countries. Paramount among them was a group in Denmark

(Witken et al., 19xx). Because the military draft is compulsory for males in Denmark,

they were able to identify virtually the entire male cohort in Denmark by examining draft

records. They selected individuals from this cohort who were taller than average (to increase the potential yield of XYY males) and genotyped a random sample of 4,139 of them. Of these, they found 12 XYY men. The researchers then searched the centralized Danish records to find all those of the 4,139 males who were registered for committing a crime. Nine percent of the normal men were so registered but 5 of the 12 XYY males (42%) were registered. This difference was significant and suggests that XYY males do, in fact, get into trouble with the law more often than normal males.

But a search for the reasons *why* these XYY males was especially illuminating. They had not been arrested for crimes of murder, rape, and general mayhem that stereotypic impression of "overtestosteronized" males might imply. Instead, their arrests and convictions were largely due to petty crimes that the authors of the study suggested might be due to a slight depression in the average IQ score of XYY individuals.

Other research on much smaller samples of XYY individuals agrees with this opinion. The emerging opinion is that XYY boys have mild learning problems and mild behavioral problems that might predispose them to act impulsively in certain situations and hence get into contact with the law. It is certainly the case that the picture of the XYY male as a hypervirilized, oversexed, aggressive sociopath has not been confirmed.

In summary then, two myths about the XYY syndrome must be disputed. The first is that these individuals have some unknown hormonal balance that makes them superaggressive and hypersexual. Although there may be mean differences between XYY

and XY males in these variables, those mean differences are likely to be quite small and unworthy of comment.

The second myth is that XYY males are entirely unremarkable and do not differ in any way from XY males. The available evidence suggests that there are important differences between these groups. The differences are not particularly large nor are they specific to interpersonal violence, aggression, and rape. Still, some XYY males have mild learning disabilities and may eventually come to the attention of the legal system.

Chromosomal Microdeletions

Prader-Willi, Angelman, and Williams syndrome are three disorders with behavioral consequences that are caused in most cases by small deletions in a chromosome. In many cases, the deletions are too small to be seen in a karyotype, so *in situ* hybridization[14] is used for diagnostic purposes. Although these syndromes are discussed as chromosomal anomalies, it is likely that they may turn out to be single gene, Mendelian disorders—it is just that the deletion of a large section of DNA is effectively knocking out a critical gene.

Prader-Willi's syndrome (PWS) and the Angelman syndrome (AS) illustrate the intriguing phenomenon of genomic imprinting. Both syndromes are caused by a deletion of DNA in a certain region of chromosome 15[15]. When the deletion comes from the

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[14] See Chapter 5 for an explanation of *in situ* hybridization.
[15] The precise area of deletion is 15q11-13 and consists of about 3.5 million nucleotides. Chromosomal rearrangements and certain gene mutations in this area may also result in these syndromes.

sperm, PWS results but when it is inherited maternally, then AS occurs. As you read the

descriptions of the syndromes pay close attention to the striking behavioral differences.

Prader-Willi Syndrome

Like all chromosomal disorders, there are a number of physical features associated

with PWS.[16] By age 3 to 7, PWS children usually develop insatiable appetites[17] and are

doubly disadvantaged because they require fewer calories than normal to gain weight.

PWS individuals often spend considerable time foraging for food and sequestering large

amounts of it. As a result, life-threatening obesity can result. The customary

intervention is to institute an exercise regimen and strict environmental controls to reduce

food availability and intake.

Cognitive development is delayed. The average IQ is around 65, but the variance

in IQ is not markedly different from normals. As a result, PWS can result in anything

from severe mental retardation to IQ well within the low normal range. Other frequent

features include *perseveration* (the repeated and often uncontrolled repetition of a phrase

or gestures), mild obsessive-compulsive rituals, intolerance of a change in daily routine,

and sleep problems (PWS people often require several naps during the day). Although

the Prader-Willi child is often talkative and friendly, he is especially prone to

stubbornness, argumentativeness, irritability, and verbal and physical aggression. Short,

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[16] PWS is characterized by a lack of muscle tone (*hypotonia* or "floppy baby"), incomplete sex development at birth (*hypogonadism* or small penis and undescended testes in males and small clitoris and labial folds in females), almond shaped eyes; downturned mouth, thin upper lip, small chin, and short stature. The hypotonia is present at birth and is often associated with suckling problems which can result in tube feeding. It typically improves after one or two years but seldom reaches normal levels.
[17] *Hyperphagia*.

but very intense tantrums and temper outbursts are common. Although the unruly

behavior is a sometimes a response to the withholding of food, it can frequently occur

without provocation.

Angelman Syndrome (AS)

Although there are striking physical symptoms characteristic of AS,[18] the

behavioral differences are the most intriguing.

Temper, eating disorder, and obesity do not characterize Angelman syndrome.

Instead, AS cases are characterized by hyperactivity, attention problems, unusual

happiness, and a failure to speak. Like all syndromes, AS differs from normal behavior

mostly in mean levels but much less in variance. Hence, there is a wide amount of

variability that can been seen in AS. AS infants often express persistent social smiling as

early as the first trimester after birth. Soon they begin to laugh, often uncontrollably, at

the proverbial drop of a hat and, in many cases, for no discernible reason.

AS cases exhibit a striking disparity in their understanding versus expression of

language. Even as adults few AS people have a vocabulary exceeding ten words, and they

often use their few words indiscriminately and without symbolic use. For example, the

word "mama" may be uttered without any reference to mother. Higher functioning AS

people may develop nonverbal communication skills by pointing, gesturing, and signing,

but even here communication is rudimentary. While formalized IQ and developmental

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[18] AS cases are often normal appearing at birth, the disorder being diagnosed after the child fails to develop
appropriately. The physical characteristics include small head circumference (*microcephaly*), inability to

testing usually suggest severe mental retardation, many clinicians are convinced that the communication deficits of AS give invalid results on standard tests and underestimate the cognitive ability of AS. High functioning adults with AS enjoy socializing and participate in the daily activities of their families.

Why do laughter and language deficits occur when maternal DNA is missing while obesity and temper present when father's DNA is missing? No one is certain at present, although remarkable progress in being made in identifying the genes responsible for these syndromes. Converging evidence is implicating the UBE3A[19] gene on chromosome 15 as the source for AS. This gene is turned off when inherited from the father, so when the gene and its surrounding area are deleted in a mutant maternal chromosome, AS results. Evidence for this view comes from some rare AS cases where the UBE3A gene is completely normal but a mutation in a prompter region effectively turns the gene off.

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focus the eyes properly (*strabismus*), and wide mouth with widely spaced teeth. Pigmentation in both PWS and AS is underdeveloped (*hypopigmentation*), often resulting in fair colored hair and eyes.
[19] UBE3A is the ubiquitin-protein ligase E3A gene.

 Need to get picture

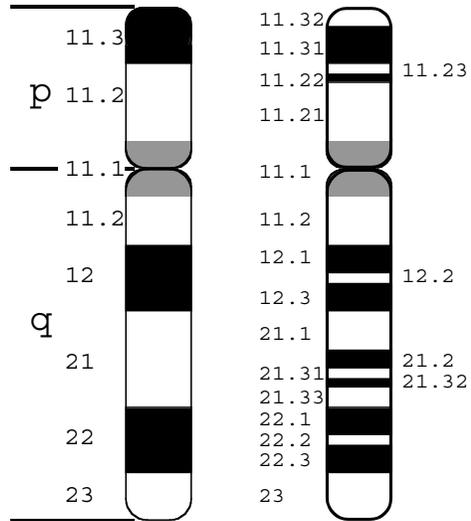Figure 8.1. A karyotype—a picture of stained chromosomes.

Figure 8.2. Chromosome bands and their nomenclatures under low resolution (left) and high resolution (right) banding.