The word *chromosome* is derived from the Greek words *chromos*, meaning color, and *soma*, meaning body. Chromosomes were discovered in the latter half of the 19th century when early cell biologists were busily staining cell preparations and examining them under microscopes. It was soon recognized that the number of chromosomes in the sperm and the 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 genetic material under the microscope, for more than 20 years early cell biologists were unable to derive the simple laws of segregation and independent assortment postulated by an obscure 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 a lymphocyte, obtained from a blood sample. Lymphocytes are kept alive, undergoing their process of division, in a culture. Then, in a series of complicated steps, they are stained and examined under a microscope. Pictures are taken of the chromosomes under a 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.

Some sections of chromosomes absorb the stain better than others, leading to a characteristic banding pattern for every chromosome. Several different staining techniques are 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 (the ISCN, or International System for Human Cytogenetic Nomenclature) 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 frequently is encountered in genetics to refer to a gene or chromosomal anomaly involving an autosome. The autosomes are ordered by length, position of the centromere (the region separating the two arms of the chromosome), and banding patterns.

Figure 8.1 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 8.1, 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 chromosome in Figure 8.1.

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 sign 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 that results in Down's 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. (See Chapter 4 on parental imprinting.)

There are many other notational devices for chromosomal anomalies, but they are too detailed for our purposes here. 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 more than 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 recognized at or shortly after birth represent the tip of an iceberg from the perspective of all human conceptions.

Three chromosomal aberrations, illustrative for their consequences, are discussed in the following sections.

Down’s Syndrome

Down’s syndrome involves inheritance of extra chromosomal 21 material. Of the three forms of Down’s syndrome, the most common, accounting for more than 95% of cases, is trisomy 21 (the inheritance of a whole extra copy of chromosome 21). The trisomy is an accident of birth and results from one of the gametes—the sperm or the egg, but usually the egg—accidentally getting two copies of chromosome 21 instead of one. Hence, this form of Down’s syndrome, 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 syndrome, 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 chromosome 21. The third, and least common, form of Down’s syndrome is mosaicism, accounting for about 1% of cases. In this form, 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 person with the mosaic form depends on the percentage of cells with the extra genes from chromosome 21.

The critical region on chromosome 21 that results in Down’s syndrome is thought to be on the long arm (i.e., q arm), specifically band 22. Considerable research is being conducted to narrow the region suspected to be problematic 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. The large number of physical features associated with Down's syndrome include flattening of the nasal bridge; epicanthal folds that give the eyes an Asian appearance; 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 (aka dermatoglyphics); and short stature. It is crucially important to recognize that few people with Down's syndrome 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. Down's cases also have delayed physical development—the Down's child often begins walking 3 to 24 months later than typical for normal children.

The brains of those affected by Down's syndrome also show the typical pathology of Alzheimer's disease, a fact that led researchers to concentrate on chromosome 21 in their search for Alzheimer's genes. About half of Down's cases over 50 years of age show demonstrable signs of dementia (Chapman & Hesketh, 2000). 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 syndrome can now live into their 50s and 60s, whereas as recently as 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 2,000 births. Risk increases gradually, so that by the early thirties it is about 1 in 750. Thereafter, there is a marked increase in risk per year of age, 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 of conceiving a Down's child. As is true for 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 and, if the results are positive, choose to abort the fetus. As a result of elective abortion, the prevalence of Down's syndrome has decreased in the past 25 years.

With few exceptions, Down's cases have mental retardation and learning disabilities (Kessler & Moos, 1973). On average, the degree of mental retardation is moderate, but the extent of cognitive impairment is remarkably variable. A rare Down's case may require institutionalization, but many can be mainstreamed in schools. Outcomes in Down's cases are clearly associated with education and family-background variables (Hauser-Cram et al., 2001; Hay, 1985), and there is some evidence that behavioral
problems are less severe in Down’s cases than in those not affected by the syndrome but with similar levels of cognitive disability (Chapman & Hesketh, 2000).

With specialized education and training, a significant proportion of Down’s cases would be able to hold jobs and be productive members of society. They might not be the neurosurgeons or the appellate judges of our society, but they, like a large number of people with mental retardation, could function well in such jobs as stocking shelves, cleaning up stores after hours, and running errands. The fact that few actually perform such work says more about our society’s willingness to train and employ these people than it does about their cognitive capabilities.

Down’s cases are real human beings. They do have differences from those born with 46 chromosomes, but they laugh, socialize, and love affection just the same. You and I have acquaintances with rough edges who can be disruptive and overbearing at times. So too can some individuals with Down’s syndrome. 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 Down’s syndrome.

The largest lesson for the behavioral scientist lies in the variability of Down’s cases. This lesson 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 (Cicchetti, 1988).

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 more than half the cases, is 45,X (also written as 45,XO); the nomenclature signifies that an entire sex chromosome is missing. About two thirds of 45,XO cases inherit their single X chromosome from their mothers (Jacobs, Betts, et al., 1990). Individuals with only part of an X chromosome, those with certain structural alteration in an X, and mosaics make up the remaining TS 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 more than 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. Physically, almost all Turner's women have short stature. Otherwise, the physical characteristics of many Turner's cases 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 (lymphedema) 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, TS women are at risk for a variety of medical complications. The most notable of these is irregular development of the ovaries (gonadal dysgenesis). As a result, a girl with Turner's syndrome fails to develop secondary sex characteristics (menstruation, breast development, and pubic hair). Fortunately, TS can be treated with hormone replacement therapy to promote adolescent growth and the development of secondary sex characteristics. The irregular development of the ovaries can also result in infertility. Many people affected by TS elect to have their ovaries surgically removed because they are at high risk for the development of ovarian cancer.

Behaviorally, the most notable feature of TS is its normality. A significant proportion of cases first came to medical attention because of concern over the absence of sexual maturation in the teenage years. This fact alone suggests that behavioral differences between TS and normal girls are not very large.

In terms of personality, there are indeed detectable differences between TS cases and normal girls in levels of maturity, social skills, and self-esteem (McCauley, Ross, Kushner, & Cutler, 1995; Ross, Zinn, & McCauley, 2000), but these differences are small relative to the overlap between the two groups. The differences do not come close to the magnitude of the behavioral differences found between normals and those with Mendelian disorders. In addition, these differences appear to diminish after growth hormone therapy increases the stature of girls affected by TS (Huisman et al., 1993; Siegel, Clopper, & Stabler, 1998).

Cognitively, TS cases have notably lower 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. Once again, the magnitude of these differences is small.

Many early clinical descriptions portray women affected by TS as having stereotypically feminine interest patterns (Money, 1970). As children, they preferred frilly dresses to jeans and enjoyed playing with dolls more than climbing trees. However, few systematic data have been gathered on this issue, and it would be unwise to generalize these clinical impressions to the present day, when gender roles have changed.
Despite the lack of an entire chromosome, TS cases grow up to be largely well-adjusted women with a range of academic and occupational outcomes typical of normal women (Aran et al., 1992; Delooz, Van den Berghe, Swillen, Kleczkowska, & Fryns, 1993). Once again, adult TS cases express problems with self-confidence and insecurity, but the differences between them and normal people are very small compared to the marked differences that occur in most genetic syndromes.

The intriguing feature of TS is why it occurs 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, speculation rests on those few genes on the X that are still active in the Barr body, but to date no one isolated which of those loci may contribute to TS.

A final—and also controversial—feature of TS is its interplay with genomic imprinting. After the phenomenon of genomic imprinting was described, it was natural to ask if any of the features of TS are associated with the maternal or paternal transmission of the single X chromosome. Some physical features, most notably height, cardiovascular anomalies, and neck-webbing, are associated with maternal inheritance of the X (Chu et al., 1994). The controversial issue arose when Skuse et al. (1997) reported that inheritance of the paternal X in TS was associated with increased cognitive skills and social adjustment. The researchers argued that there might be an imprinted gene on the X chromosome that contributes to social cognition. This locus would be silenced when inherited from the mother but activated when transmitted by the father. This is an exciting development in behavioral genetics, but the initial finding awaits replication in other labs.

**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 nonviable 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 they would pass as completely normal individuals throughout life. Their faces are not irregular (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. Jacobs and colleagues (Jacobs, Brunton et al., 1965) reported an increased frequency of XYY individuals in an institution for dangerous criminal offenders. A number of other research groups reported similar results in other institutions (see Hook, 1973, for a review of the literature of that time). A flurry of speculation following these empirical reports suggested, either overtly or between the lines, that the inheritance of an extra Y chromosome “overmasculinized” 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.

Several research groups were ready to embark on such an endeavor, but they encountered a strong backlash from other scientists. Because of fears that identifying these boys at birth and labeling them as antisocial might create a self-fulfilling prophecy, research in the United States was effectively stopped in its tracks.

This controversy influenced research in the United States but left the question open for scientists in other countries. Paramount among them was a group in Denmark (Witkin et al., 1976). Because the military draft is compulsory for males in Denmark, these researchers 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. Of the normal men, 9% 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 do normal males.

A search for the reasons why these XYY males were more prone to law-breaking behavior was especially illuminating. They had not been arrested for crimes of murder, rape, and general mayhem that a stereotypic impression of "overestrogenized" males might imply. Instead, their arrests and convictions were largely due to petty crimes. The authors of the study suggested that this result 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 (Gotz, Johnstone, & Ratcliffe, 1999; Robinson, Bender, & Linden, 1990; Theilgaard, 1984). The emerging view 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 law enforcement authorities. It is certainly the case that the picture of the XYY male as a hypertrophied, 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 aggressiveness and sexuality, those mean differences are likely to be small.

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 syndrome, Angelman syndrome, 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 is used for diagnostic purposes. (See Chapter 7 for an explanation of in situ hybridization.) Although these syndromes are discussed as chromosomal anomalies, some 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 syndrome (PWS) and the Angelman syndrome (AS) illustrate the intriguing phenomenon of genomic imprinting. Both syndromes are caused by a deletion of DNA in the same region of chromosome 15.\(^9\) When the deletion comes from the 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

As for all chromosomal disorders, a number of physical features are associated with PWS.\(^{11}\) However, the behavioral features associated with PWS are by far more interesting (Dykens & Kasari, 1997; van Lieshout, De Meyer, Curfs, & Fryns, 1998a; van Lieshout, De Meyer, Curfs, Koot, et al., 1998b). By age 3 to 7, PWS children usually develop insatiable appetites (hyperphagia) 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, and the variance in IQ is reduced—but not markedly so—from that of normals. As a result, PWS can result in anything from severe mental retardation to an 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 PWS child is often talkative and friendly, he is especially prone to stubbornness, argumentativeness, irritability, and verbal and physical aggression. Short but very intense tantrums and temper outbursts are common. Although the unruly behavior is sometimes a response to the withholding of food, it can frequently occur without provocation. Many of these behavioral characteristics extend into adulthood (Clarke, Boer, Chung, Sturmey, & Webb, 1996).

Angelman Syndrome

Although there are striking physical symptoms characteristic of AS,\(^{12}\) the behavioral abnormalities are the most intriguing. The temper, eating
disorder, and obesity found in those affected by PWS do not characterize those with Angelman syndrome. Instead, AS cases are marked by hyperactivity, attention problems, unusual happiness, and a failure to speak (Penner, Johnston, Faircloth, Irish, & Williams, 1993; Zori et al., 1992). 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 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 people with AS have a vocabulary exceeding 10 words, and they often use their few words indiscriminately and without symbolic meaning. For example, the word “mama” may be uttered without any reference to a mother. Higher-functioning people with AS may develop nonverbal communication skills such as pointing, gesturing, and signing, but even here communication is rudimentary. Although formalized IQ and developmental testing usually suggest severe mental retardation, many clinicians are convinced that the communication deficits of AS lead to invalid results on standard tests and underestimate the cognitive ability of people with 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, whereas obesity and temper present when paternal 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 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 in which the UBE3A gene is completely normal but a mutation in a promoter region effectively turns the gene off.

**CONCLUSION**

The brief overview given here does little justice to the large number of different chromosomal aberrations and syndromes that researchers have described. The interested reader is referred to current textbooks on medical genetics as well as to the increasing number of Web sites devoted to these syndromes.
1. Lymphocytes are actually colorless cells formed in the lymph nodes, in the spleen, and in 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, a chemical such as colchicine or colcemid is added to arrest cell division at a crucial stage (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. Here the cells are in the prophase stage of cell division.

4. Denser banding comes from chromosomes in the metaphase stage.

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

6. In earlier times, the term *Mongolism* was used to describe Down’s syndrome because of the appearance of the eyes of afflicted people.

7. Neurofibrillary 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).

8. Usually performed between week 15 and week 17 of pregnancy, amniocentesis involves the insertion of a needle into the sac surrounding the fetus and extraction of a fluid sample (amniotic fluid from the 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 week 12 of pregnancy.

9. The natural course of sex development in humans is female. It takes the presence of a Y chromosome to masculinize a developing fetus.

10. 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 (Nichols & Knepper, 2001; Repetto, 2001).

11. PWS is characterized by a lack of muscle tone (*hypoatonia* 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 hypoatonia is present at birth and is often associated with sucking problems that can necessitate tube feeding. It typically improves after 1 or 2 years but seldom reaches normal levels.

12. AS cases often appear normal at birth, with the disorder being diagnosed after the child fails to develop appropriately. The physical characteristics include small head circumference (*microcephaly*), inability to focus the eyes properly (*strabismus*), and wide mouth with widely spaced teeth. Pigmentation in both PWS and AS is underdeveloped (*hypoatination*), often resulting in fair colored hair and eyes.

13. UBE3A is the ubiquitin-protein ligase E3A gene.
REFERENCES


