Topic Page: Chromosome abnormalities

Definition: **Chromosomal Abnormality** from *The SAGE Glossary of the Social and Behavioral Sciences*

Abnormalities exist when chromosomes exhibit atypical numerical properties (i.e., there is more than or less than one pair of chromosomes) or structural properties (i.e., there is extra chromosomal material, or a fraction of the chromosome is missing). Such abnormalities can lead to conditions such as Down syndrome, mental retardation, autism, or Turner's syndrome. Although some chromosomal abnormalities are believed to be inherited, most are purely accidental and occur during the conception or gestation process.

Image from: **Chromosomes There are 23 pairs of...** in *Conception, Pregnancy & Birth: The Childbirth Bible for Today's Parents*

Summary Article: **Chromosomes, Human Anomalies, and Cytogenetic Abnormalities**
From *Encyclopedia of Special Education: A Reference for the Education of Children, Adolescents, and Adults with Disabilities and Other Exceptional Individuals*

Chromosomal (cytogenetic) abnormalities are the most frequent cause of congenital (present at birth) malformations, affecting some 1 in 200 newborns (Moore,). Their importance is reflected in the fact that they account for at least 10 to 15% of individuals with mental retardation severe enough to require institutionalization (Moore,; Pueschel,) and for about 8 to 10% of newborn and early infant deaths (Sperling,). Further, some 30% of spontaneously aborted embryos/fetuses had a chromosomal abnormality, an incidence 50 times higher than that in live births, meaning that incidence in all pregnancies must be about 5% (Sperling,).

Because chromosomal abnormalities involve disruption in the action of many genes, most are associated with severe and varied effects (Brown,). These frequently, but not always, involve general and specific intellective deficits, particular facial anomalies, and cardiovascular, digestive, and pulmonary defects. Further, people with chromosomal abnormalities usually have such characteristic phenotypes (physical appearance and physiological and behavioral functioning) that they frequently look more like unrelated persons with the same chromosomal abnormality than like their own siblings (Dobyns,; Moore,). The common characteristics that differentiate individuals with one abnormality from normal people or those with a different abnormality are called syndromes. Some two-dozen chromosomally based syndromes have been identified. Although some, particularly the familiar Down, Klinefelter, and Turner syndromes are relatively common, others are so rare that only 50 or so cases have been reported (Smith,).

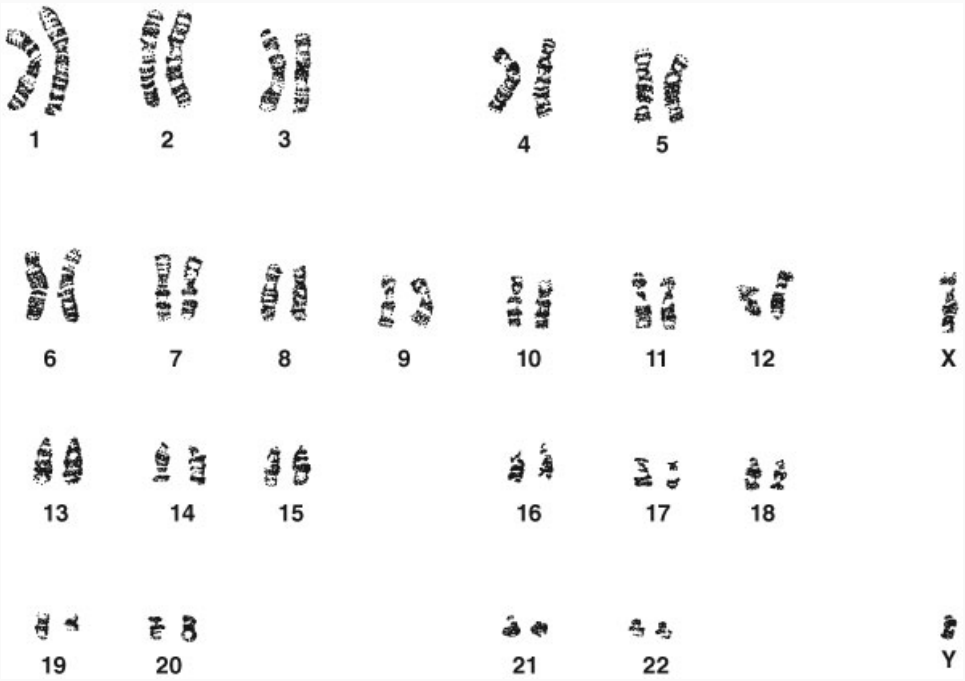
This entry will address general issues about abnormalities, provide background information for more specialized reading, and address similarities and differences among currently identified syndromes. As is the case with other genetically based disorders and congenital and perinatal abnormalities, new research routinely leads to significant changes in knowledge.

(Vogel and Motulsky, p. 18) elegantly describe human cytogenetics as “a successful late arrival.” Although the chromosome theory of inheritance had been proposed in 1902, cytogenetics really began in 1956 with the discovery that the diploid number of human chromosomes was 46 instead of the commonly accepted 48. To give an idea of past attitudes toward the handicapped and their behavior, the diploid number 48 had been found by (Painter) in studies of spermatogenesis in testes of three

inmates of the Texas State Insane Asylum who had been castrated because of, among other things, their excessive masturbation. When in 1959 researchers discovered chromosomal bases for three common and well-established human syndromes (Down, Klinefelter, and Turner), human cytogenetics really came into its own. Since then, a variety of chromosomally based syndromes have been discovered on the basis of now-routine cytogenic analysis of spontaneously aborted fetuses, early death newborns and infants, and individuals with physical and behavioral abnormalities. A number of children traditionally labeled by diagnosticians as “syndromish in appearance” (something looks wrong but no etiology is known) now are identified as having a chromosomal abnormality. In most cases, the description of the physical and behavioral characteristics of the syndrome has followed, rather than preceded, chromosomal analysis. Further, subsequent studies have identified multiple chromosomal bases for syndromes such as Down, Klinefelter, and Turner that help to account for high variability among and even within affected individuals. A variety of technical advances account for much of our knowledge about these abnormalities (Dobyns,; Sperling,; Vogel & Motulsky,).

Normal and Abnormal Karyotypes

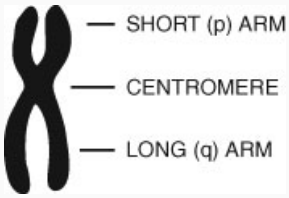
Normal humans have 23 pairs of chromosomes in all body cells, 22 pairs of autosomes, and one pair of sex chromosomes. Females normally have two long X sex chromosomes and males one long X and one shorter Y sex chromosome. Chromosomes (colored bodies) are visible only early in mitosis, when cell samples are subjected to certain stains. A *karyotype* is a picture of chromosomes arranged by pair. The 22 autosomal pairs are arranged from the longest (1) to the shortest (22), followed by the sex chromosomes. A karyotype, showing chromosomal bands, of a normal human male is shown in Figure. Figure shows a typical chromosome pair; the short arm is termed “p” and the long arm, “q”; the two arms are held together at the centromere, or primary constriction. (Cohen and Nadler) suggest the useful mnemonic of associating “p” with petite. Chromosomes are grouped into three types: metacentric (e.g., numbers 1 and 3), where the arms are nearly equal in length; submetacentric (e.g., numbers 4 and 5), where the p arm is distinctly shorter than the q; and acrocentric (e.g., numbers 14 and 21), which have a secondary constriction and abbreviated and apparently genetically inactive satellite p arms.



C.11 Karyotype for a normal human male. Twenty-two pairs of autosomes have been ordered and numbered

according to convention from largest to smallest. Sex chromosomes are labeled X and Y.

Source: (Cohen and Nadler).



C.12 Standard nomenclature for describing parts of a chromosome, after (Cohen and Nadler).

Source: (Cohen and Nadler).

Normal Cell Division

During mitosis, the process of duplication of body cells, each of the 46 chromosomes divides and one member of each migrates to a pole of the cells. When the cell divides, each offspring cell contains the same 23 pairs of chromosomes. Thus mitosis is a process of chromosome duplication. In meiosis, the process of production of germ cells (sperm and eggs), each of the 23 chromosome pairs divides and one member of each pair migrates to a pole of the cell. When the cell divides, each offspring has 23 chromosomes. Thus each germ cell has 23 chromosomes. Meiosis is a process of chromosome reduction. Women's eggs will all have 22 autosomes and an X chromosome; men's sperm all have 22 autosomes and can have either an X or a Y. In sexual recombination, when a sperm penetrates an egg, the resulting zygote normally has the appropriate 46 chromosomes. Thus, gender of offspring is determined by the father's sperm.

Abnormal Karyotypes

Abnormalities can be: (1) an abnormal total number of chromosomes in an individual's body cells; (2) structural aberrations resulting from breakage in one or more chromosomes; or (3) populations of cells of different chromosome numbers in the same individual (mosaicism).

Aneuploidies refers to deviations, greater or fewer, in number of chromosomes from the normal 46. The most common aneuploidy is trisomy 21, which accounts for the greatest number of chromosomal abnormalities in spontaneous abortions as well as in live births. Trisomies on most pairs are prenatally lethal. Similarly, monosomy, absence of one of a pair, resulting in fewer than 46 chromosomes, is virtually always prenatally lethal, except for Turner's syndrome, in which one X chromosome is missing (45,X). Even then, only one in 150 to 200 45,X embryos survives to full-term birth. The most common cause of aneuploidy is nondisjunction, the failure of a chromosome pair to split during formation of germ cells in meiosis. Thus, one offspring germ cell will have a "double dose" of one chromosome and the other will have none. Anaphase lag can also produce monosomy.

Mosaicism results from nondisjunction occurring mitotically in a cell in an embryo in an early stage of development. As a result, if the embryo survives and continues to develop, it will have both normal and abnormal, generally trisomic, cell populations. Because of the presence of normal cells, individuals with mosaicism will generally show less severe symptoms than those with the pure syndrome.

The basis for nondisjunction is not known, but is presumed to be manifested biochemically. In nondisjunction Down syndrome, approximately 80% of the cases result from maternal and 20% from paternal nondisjunction (Sperling,). Since all autosomal trisomies (not just Down syndrome) increase

dramatically with maternal age, research focuses on factors that correlate with aging, including potential problems with aging oocytes themselves. Hypothesized links with irradiation, chemical agents, methods of birth control, and endocrine factors have not been fully confirmed, but some evidence suggests they play a role (Hassold & Jacobs,).

Chromosomes may break, with material being either lost or attached to another chromosome. The most common structural aberrations are translocations, which result when two chromosomes break and parts of one are transferred to another. A reciprocal translocation occurs when two nonhomologous chromosomes exchange pieces. Individuals with such translocation chromosomes themselves have an appropriate balance of chromosomes and are phenotypically normal. Since they are carriers of a translocation chromosome, their offspring may suffer from duplication-deficiency syndromes, notably partial trisomies.

Important because of clinical implications are centric fusions, or Robertsonian translocations. Centric fusion occurs when two acrocentric chromosomes each break near the centromere and rejoin. Generally, the short arms of both and the centromere of one are lost. Again, individuals may be unaffected, although they have one-fewer-than-normal chromosome, but they are carriers. Their offspring may have a trisomy syndrome. Monosomies are also possible, but appear to be prenatally lethal. The best-known translocation is Down syndrome, resulting from centric fusion of chromosome 21 with chromosome 14 or, less frequently, 15.

Several other structural aberrations also may occur. Simple loss of part of a chromosome may result in a deletion syndrome. Isochromosomes occur when instead of a chromosome pair dividing longitudinally through the centromere, it divides horizontally, producing two chromosomes with identical arms. Fertilization will produce a cell with three p or q arms and only one of the other. When the segment between two breaks in a chromosome becomes inverted, reversing the gene order, an inversion results. Ring chromosomes occur when both ends of a chromosome break off and the tips of the centric segment rejoin. The resulting circular chromosome is unstable and has material from both ends deleted.

Standard Nomenclature

Normal and abnormal human karyotypes are described using a standard system, general aspects and examples of which are given here. More detailed descriptions are in (Cohen and Nadler), (Smith), (Vogel and Motulsky), and most human genetics textbooks.

The order of information is (1) total number of chromosomes; (2) sex chromosomes; and (3) any abnormalities. Extra or missing chromosomes are indicated by “+” and “–”, respectively, before the affected chromosome’s number; extra or missing parts are indicated by “+” and “–”, respectively, after the affected part. Structural aberrations are indicated by a standard abbreviation followed, parenthetically, by the number of the affected chromosome(s). Then, also parenthetically, the affected arm(s) and, if known, the chromosomal band numbers, are stated. Mosaics are indicated by a (/) mark separating descriptions of the two cell populations.

Abnormalities and Their Characteristics

Although chromosomal syndromes vary widely in their effects, the various types share some characteristics. Because much genetic material either has been added or is missing, many are lethal and most of the rest involve multiple and severe complications. However, as normal individuals vary in their

physical and behavioral characteristics, so do those affected by chromosomal abnormalities. Not all will show even all of the major effects.

It is important that different sources vary in their estimates of incidence and specification of major characteristics. In a number of cases, subsequent cases have led to changes in what were initially thought to be defining characteristics. For example, Cat-eye syndrome (trisomy 22p) was named for the striking coloboma of the iris seen originally. However, it has occurred only in a minority of the 40 cases that had been reported at the time of (Smith's summary).

Chromosomal Aneuploidies

The most common abnormalities are aneuploidies, involving an added or missing chromosome. Multiple forms of some may occur. By far the most common is Down syndrome (trisomy 21), but several others have been reported. Early death is common in all, and in some types virtually all die in early infancy. Although each has individual characteristics, all involve brain damage generally resulting in moderate to severe mental retardation, congenital heart disease, and malformed ears. Specific facial, limb, and digit abnormalities are also common. All increase dramatically in incidence with maternal age (Vogel & Motulsky,).

Turner and Klinefelter syndromes have clear phenotypic characteristics and were described before the development of modern cytogenic techniques. Both are associated with absence of puberty and sterility. Unfortunately, as pointed out by (Brown), textbook authors have frequently described sex-chromosome aneuploidies in chapters on mental retardation. However, standard forms are associated with low average intelligence (IQ > 90), not mental retardation, although incidence of mental retardation is higher than among the normal population. Many affected individuals will complete high school and college. Mosaic Turner females and Klinefelter males will be less affected. Klinefelter males and Poly-X females with extra X chromosomes above trisomy for sex chromosomes are much more adversely affected and likely to be retarded (Korf,).

Klinefelter and Poly-X syndromes increase with maternal age (Hassold & Jacobs,). However, incidence of neither Turner nor XYY syndrome correlates with maternal age, consistent with largely paternal origin (Hassold & Jacobs,; Simpson,).

Abnormal Parts of Chromosomes

Several partial trisomy syndromes, involving extra chromosomal material, and deletion syndromes are known. Mental retardation of some degree is common to all. Low birthweight and specific facial and digital anomalies are also frequent.

Of particular current interest is Fragile X syndrome, resulting from a constriction in the X chromosome, which cytogenic studies reveal to be relatively common. Associated with mental retardation in affected males, it appears to be second only to Down syndrome as a cytogenic cause of mental retardation.

Human Genome Project

The Human Genome Project (HGP) was the international, collaborative research program whose goal was the complete mapping and understanding of all the genes of human beings. All our genes together are known as our *genome*. The HGP was the natural culmination of the history of genetics research.

The HGP has revealed that there are probably somewhere between 30,000 and 40,000 human genes. The completed human sequence can now identify their locations. This ultimate product of the HGP has

given the world a resource of detailed information about the structure, organization, and function of the complete set of human genes. This information can be thought of as the basic set of inheritable "instructions" for the development and function of a human being.

The International Human Genome Sequencing Consortium published the first draft of the human genome in the journal *Nature* in February 2001 with the sequence of the entire genome's 3 billion base pairs some 90% complete. A startling finding of this first draft was that the number of human genes appeared to be significantly fewer than previous estimates, which ranged from 50,000 genes to as many as 140,000. The full sequence was completed and published in April 2003.

Upon publication of the majority of the genome in February 2001, Francis Collins, the director of the National Human Genome Research Institute (NHGRI), noted that the genome could be thought of in terms of a book with multiple uses. The tools created through the HGP also continue to inform efforts to characterize the entire genomes of several other organisms used extensively in biological research, such as mice, fruit flies, and flatworms. These efforts support each other, because most organisms have many similar, or *homologous*, genes with similar functions. Therefore, the identification of the sequence or function of a gene in a model organism, for example, the roundworm *C. elegans*, has the potential to explain a homologous gene in human beings, or in one of the other model organisms.

This ambitious project required a variety of new technologies that made it possible to construct a first draft of the human genome relatively rapidly. These techniques included: DNA Sequencing, the Employment of Restriction Fragment-Length Polymorphisms (RFLP), Yeast Artificial Chromosomes (YAC), Bacterial Artificial Chromosomes (BAC), the Polymerase Chain Reaction (PCR), and Electrophoresis.

Of course, information is only as good as the ability to use it. Therefore, advanced methods for widely disseminating the information generated by the HGP to scientists, physicians, and others is necessary to ensure the most rapid application of research results for the benefit of humanity. Biomedical technology and research are particular beneficiaries of the HGP.

However, the momentous implications to individuals and society from possessing the detailed genetic information made possible by the HGP were recognized from the outset. Another major component of the HGP—and an ongoing component of NHGRI—is, therefore, devoted to the analysis of the ethical, legal, and social implications of the newfound genetic knowledge and the subsequent development of policy options for public consideration (National Human Genome Research Institute,).

Implications for Special Educators

As cytogenic analyses become more standard, increasing numbers of children will be identified as having some chromosomal disorder. Many minor ones will have few implications for teachers. Others will be associated with general and specific intellectual deficits, coordination problems, and emotional disorders. Special educators and others in education generally may need to become familiar with the syndrome and standard nomenclature. Further, research will doubtless render some current knowledge incorrect and we must be ready to accept new information. It should be kept in mind that syndromes can induce stereotypes, and that affected children should be treated on the basis of their individual characteristics, not the general ones of a syndrome.

Related Articles

See also Cri du Chat Syndrome; Down Syndrome; Etiology; Fragile X Syndrome; Klinefelter's Syndrome;

Turner Syndrome; XYY Syndrome

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Brown, Robert T. "Chromosomes, Human Anomalies, and Cytogenetic Abnormalities." *Encyclopedia of Special Education: A Reference for the Education of Children, Adolescents, and Adults with Disabilities and Other Exceptional Individuals*, edited by Cecil R. Reynolds, et al., Wiley, 4th edition, 2013. *Credo Reference*, https://search.credoreference.com/content/topic/chromosome_abnormalities. Accessed 18 Sep. 2019.