12

Abnormal Phenotypes Due to Autosomal Aneuploidy or Polyploidy

Only three autosomal trisomies, those for chromosomes 13, 18, and 21, occur with an appreciable frequency in liveborn infants, and only one, trisomy 21, is compatible with long-term survival in a large proportion of cases. Trisomy 21, trisomy 18, and trisomy 13 produce three different and characteristic syndromes despite some degree of overlap. Traits they share include mental retardation, congenital heart defects, malformations in other organ systems, seizures, and growth retardation. These features are also common with other chromosome imbalances. For example, a ventricular septal defect is found in 47% of infants with trisomy 13, in 34% of 18-trisomics, and in 20% of 21-trisomics (Lewandowski and Yunis, 1977). In general, no single trait is exclusive to a particular chromosome imbalance, but a few tend to be associated with a particular chromosome imbalance, such as the persistence of fetal hemoglobin and abnormal neutrophil projections in trisomy 13. The increasingly routine use of

O. J. Miller et al., *Human Chromosomes*

ultrasound sometimes identifies fetal abnormalities at a stage of pregnancy at which a rapid decision is needed if termination of pregnancy is an option. Interphase FISH with DNA probes for chromosomes 13, 18, 21, X, and Y permits rapid diagnosis of aneuploidy of any of these chromosomes, or of polyploidy (Gersen et al., 1995).

Trisomy 21 and Down Syndrome

Down syndrome is the least severe of the autosomal trisomy syndromes. It is described in detail in many books and reviews, because it is the most common genetic cause of mental retardation and multiple congenital anomalies (for example, Epstein, 1995; Gardner and Sutherland, 1996). Down syndrome is characterized by moderate mental retardation, hypotonia, short stature, short extremities, oblique palpebral fissures, epicanthic folds, Brushfield spots in the irises of the eye, flat nasal bridge, open mouth, protruding tongue, small head, flat occiput, transverse palmar creases, and abnormal dermatoglyphic (palm- and fingerprint) patterns. Congenital heart disease (especially an endocardial cushion defect) is seen in about 40% and duodenal atresia, tracheo-esophageal fistula, or other gastrointestinal abnormality in about 5%. A clinical diagnosis can be made with over 95% accuracy in expert hands but only 75% overall. Ultrasound findings of a short femur and increased nuchal transparency (due to an abnormal accumulation of fluid at the nape of the neck), especially if accompanied by elevated maternal serum α-fetoprotein (of fetal origin), has led to the prenatal diagnosis of Down syndrome by chromosome studies (Verdin et al., 1997).

Mental retardation is almost universal in Down syndrome. There is usually a steady and fairly rapid decline in intellectual performance, with average IQs falling from over 75 at 1 year of age to less than 30 in those over 11 years of age. The IQ rarely stays above 80, even with early intervention and environmental enrichment. Neuronal degeneration identical to that in Alzheimer disease is frequent in middle-aged adults; cataracts and keratoconus are fairly common and may affect vision. Life expectancy now exceeds 60 years in those without congenital heart disease. The major causes of death in Down syndrome are severe congenital heart disease, cancer, and infections. There is a 20-fold increased risk of developing leukemia, and an excess of certain other tumors, particularly male germ cell tumors. Males with Down syndrome are more at risk for tumor development than females, for unknown reasons (Satge et al., 1998).

The chromosomal cause of Down syndrome, trisomy 21, was discovered by Lejeune et al. (1959). It is by far the most frequent of the autosomal trisomy syndromes, the usual estimate of its incidence being about 1 in 750 newborns. Trisomy 21 is twice as prevalent at 10 weeks of gestation as in newborns, indicating that half of those who survive the first 10 weeks of fetal life die between 10 weeks and birth (Snijders et al., 1995). In 93–96% of individuals with Down syndrome, the chromosome constitution is 47,+21. An additional 2–3% of subjects are mosaics, with a disomic and a trisomic cell line. Trisomy 21 mosaicism with minimal effects on the phenotype is sometimes found, particularly in parents of children with trisomy 21. Even gonadal mosaicism (limited to the germline) in a parent may account for the birth of a child, or more than one, with Down syndrome. In the remaining 2–5% of subjects, the extra chromosome 21 is part of a Robertsonian translocation chromosome or, rarely, a reciprocal translocation. Aberrant meiotic segregation in reciprocal translocation carriers (Chapter 16) can lead to duplication of a segment of chromosome 21 and to Down syndrome.

Trisomies corresponding to trisomy 21, in both phenotype and karyotype, are found only in the great apes (chimpanzee, gorilla, and orangutan). However, duplication (partial trisomy) of the segment of mouse chromosome 16 that is homologous to a particular segment of human chromosome 21 produces some phenotypic features of Down syndrome (Chapter 15; Reeves et al., 1995; Sago et al., 1998). Attempts to define a critical region of chromosome 21 containing genes whose extra dosage is responsible for the characteristic phenotype are described in Chapter 15.

How does the presence of a third copy of a chromosome lead to phenotypic abnormalities? The most likely reason is that the extra dosage of one or more genes on the chromosome is responsible. Some of the likely candidates are discussed in Chapter 15. It is important to remember that a gene may have an enhancing effect or an inhibitory effect. There is evidence that trisomy 21 has important inhibitory effects on genes scattered throughout the genome. Amiel et al. (1998) used FISH to analyze the replication timing of four genes: *TP53* and *HER2* on chromosome 17, *RB1* on chromosome 13, and *MYC* on chromosome 8. The two alleles of each gene replicated synchronously in normal cells but very asynchronously in 21-trisomic cells, suggesting that one allele may have been inactivated. If the two tumor suppressor genes *TP53* and *RB1* are indeed inactivated in some cells, this may be responsible for the increased risk of leukemia and certain other tumors (Chapter 28). Alleles at some loci on other chromosomes show asynchronous replication in trisomy 13 and 18, just as they

do in trisomy 21. This suggests that the inactivation of the same genes on other chromosomes is responsible for some of the phenotypic overlaps of these three trisomies (Amiel et al., 1999).

Trisomy 18 and Edwards Syndrome

Edwards et al. (1960) reported the first case of what we now call trisomy 18 syndrome. This syndrome is marked by severe neurological and cardiac anomalies, plus defects in many other organ systems. Dysmorphic features include abnormal facies; small jaw; prominent occiput; clenched, overlapping fingers; muscle rigidity; and rocker-bottom (calcaneovalgus) feet (Hodes et al., 1978). Nuchal translucency can be detected by ultrasound in 90% of 11- to 14-week-old trisomy 18 fetuses. Cytogenetic diagnosis can then be made on chorionic villus samples. The parents in these cases usually decide to terminate the affected pregnancy (Hyett et al., 1995).

The incidence of trisomy 18 is about 1 per 6000 in the newborn. It is 85 times as prevalent at 10 weeks of gestation as in newborns, indicating that over 98% of those alive at 10 weeks of gestation die before birth (Snijders et al., 1995). Of those born alive, 30% die within one month and only 10% survive 1 year (Gorlin, 1977). About 80% of the patients have straight trisomy, another 10% are mosaics, and the rest have a translocation. In one case, the karyotype was 46,XY,−18,+psu dic(18)(qter→cen→p11.31::p11.31→psu cen→qter), as verified by multicolor PRINS analysis using chromosome 18–specific α-satellite and telomeric oligonucleotide primers. The subject was monosomic for two maternal 18p12 markers, indicating that the pseudodicentric chromosome 18 was paternal in origin. Both parents had normal karyotypes, so the rearranged chromosome arose either in the father's germline or in an early cleavage division (Graveholt et al., 1997).

Trisomy 13 and Patau Syndrome

Patau et al. (1960) first reported a case of what we now call trisomy 13 syndrome (Fig. 12.1). The frequency of trisomy 13, usually an embryonic lethal condition, is 100 times greater in spontaneously aborted embryos or fetuses than in liveborns. The incidence of trisomy 13 (47,+13) in liveborns is about 1 in 12,000 (Hook, 1980). Increased maternal age is a factor in trisomy 13, as it is in other

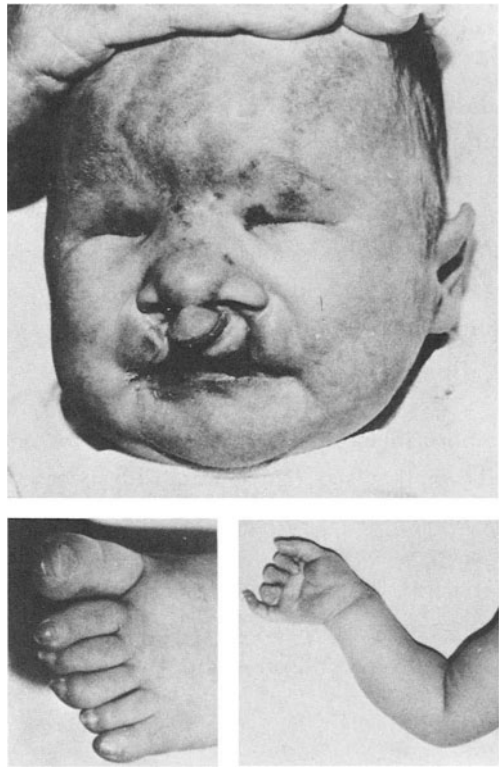

Figure 12.1. An infant with trisomy 13 (Patau) syndrome. Note the anophthalmia, cleft lip, and six toes.

trisomies. Even those infants with trisomy 13 who survive birth have a limited life expectancy; about 45% die within the first month, 90% are dead before 6 months, and fewer than 5% reach the age of 3 years. Two exceptional 13-trisomics lived for 11 and 19 years (Redheendran et al., 1981).

Infants with trisomy 13 show severe neurological impairment, with holoprosencephaly (forebrain defects, absence of the corpus callosum or olfactory bulbs), eye anomalies ranging from anophthalmia (absence of eyes) to microphthalmia, coloboma (fissure) of the iris, cleft lip, cleft palate, capillary hemangiomata, scalp defects, postaxial polydactyly, and rocker-bottom feet. Several types of complex heart anomalies are common (Hodes et al., 1978). Individuals with trisomy 13 show considerable phenotypic variation even when mosaicism is absent; so do patients with other chromosomal abnormalities.

Other Autosomal Aneuploidy Syndromes

In general, trisomy for any autosome except 21, 18, or 13 is an embryonic lethal condition. Survival until after birth is rare, with the possible exception of number 22. Despite numerous reports of 22-trisomic survivors (for instance, Kukolich et al., 1989), the extra chromosome usually appears to have arisen by 3:1 segregation in a t(11;22)(q23;q11) translocation carrier or heterozygote and is not a normal chromosome 22 (Zackai and Emanuel, 1980). No carrier of a Robertsonian translocation involving chromosome 22 (Chapter 27) has had offspring with translocation trisomy 22, and this speaks against the viability of trisomy 22.

Monosomy in liveborn infants has been established for only one autosome, chromosome 21, and even that is extremely rare, with six cases reported by 1983 (Wisniewski et al., 1983). It is also infrequent in spontaneous abortions. Monosomy 21 has never occurred among the progeny of a Robertsonian translocation heterozygote (Chapter 16). Haploid newborns or abortuses have never been seen. If haploid zygotes are ever produced, they presumably die before the time of implantation, just like most monosomic and some trisomic zygotes, so there is no recognized pregnancy.

Trisomy/Disomy Mosaicism

Mosaics with trisomic and disomic cell lines usually arise from a trisomic zygote. Subsequent loss of one of the three homologues from one cell gives rise to the disomic line. The disomic line is usually normal; the exceptions, which involve uniparental disomy and imprinting effects, are discussed in Chapter 21. The most common type of autosomal mosaicism involves chromosome 21. About 2–3% or more of individuals with Down syndrome are trisomy 21/disomy 21 mosaics. The proportion of disomic cells varies greatly, and so does the phenotype, which ranges from severe Down syndrome to complete normality. An unknown number of mosaics go undetected, either because the phenotype is normal or because disomic cells are rare in the tissues examined. Parental mosaicism plays an important role in the origin of 21-trisomic individuals: 2.7% have a mosaic parent (Uchida and Freeman, 1985). Mosaics have a much increased risk of producing 21-trisomic offspring and are responsible for some of the 21-trisomics born to young mothers (James et al., 1998).

Mosaicism for chromosome 18 or 13 is found in perhaps 2–10% of those with the corresponding syndromes and has the same moderating effect on the phenotype as noted for chromosome 21. Such mosaicism probably accounts for the rare individuals with these syndromes who survive well past infancy. Does this same moderating effect enable trisomy/disomy mosaics for other autosomes or triploid/diploid (mixoploid) mosaics to survive instead of ending in early abortion? Yes, but not very often. Rarely, an individual case report of such mosaicism has been published. About half the autosomes have been involved, in addition to triploidy/diploidy (Lin et al., 1998). Mosaicism involving chromosome 8 occurs considerably more frequently. Riccardi (1977) was able to describe over 60 cases and to characterize the phenotype. The origin of trisomy 8 mosaics appears to be different from that of most mosaics or trisomies: 20 of 26 arose postzygotically, during early embryonic mitoses, and only two of the 26 arose by maternal meiotic nondisjunction, in sharp contrast to most trisomics and mosaics (Karadina et al., 1998). More complex mosaics rarely occur, such as a severely affected individual with 13-trisomic, 18-trisomic, and normal cell lines (Wilson et al., 1983).

Mosaicism is sometimes detected in cultured second-trimester amniotic fluid cells, and even more frequently in cells cultured earlier in pregnancy from first-trimester chorionic villi, despite the absence of the abnormal cell line in the fetus or newborn. This is called *confined placental mosaicism* and is sometimes associated with abnormalities due to uniparental disomy (Chapter 21). Clinical cytogeneticists must be very careful in evaluating such cases, taking the method of ascertainment into account. If advanced maternal age is the indication, then the prognosis (expected outcome) for pregnancies with confined placental mosaicism is good. That is not the case if amniocentesis is performed in a woman because of abnormal maternal serum α-fetoprotein or maternal serum human chorionic gonadotropin values. A series of 11 women with these findings, nine under age 35, had trisomy 16 mosaicism. At least nine of the fetuses had serious complications, including intrauterine growth retardation and congenital malformations, two dying neonatally (Hsu et al., 1998).

Triploidy and Tetraploidy

The only types of polyploidy found in humans are triploidy (3n) and tetraploidy (4n). Most polyploid embryos die early in pregnancy and are spontaneously aborted. Triploidy is one of the major causes of spontaneous abortions (Chapter

11), accounting for about 17% of cases (Carr and Gedeon, 1977). Only about one in 10,000 triploid zygotes leads to a live birth. Most of these liveborns die within a day, although some have survived for a few months. In such rare cases, one tends to suspect undetected mosaicism, especially since most presumed polyploid infants have been shown to have a diploid cell line as well; they are thus *mixoploid*. They may have malformations discernible prenatally (Lin et al., 1998). The phenotype of triploids is not characteristic but includes growth retardation and multiple malformations. Rapid prenatal diagnosis of triploid fetuses is readily achieved using FISH with multiple chromosome-specific probes (Gersen et al., 1995).

Tetraploidy is rarer than triploidy among both spontaneous abortuses and liveborn infants, due either to the production of fewer triploid zygotes or to their greater lethality. Nonmosaic tetraploidy has been reported in a few newborns and in a 22-month-old girl (Lafer and Neu, 1988). In addition, a few liveborn infants have been diploid/tetraploid mosaics, or mixoploids. Malformations of multiple organ systems may be seen, but there is not a clearly defined syndrome.

Spontaneous Abortions, Fetal Deaths, and Stillbirths

Spontaneous abortions represent pregnancies that have ended prematurely because of death of the embryo or fetus, placental inadequacy, or uterine pathology. Spontaneous abortions have many causes, including hormonal, infectious, vascular, and genetic, including chromosomal. It is therefore rather surprising that almost half of first-trimester spontaneous abortions are caused by chromosome abnormalities (Chapter 11). Early abortions have a higher frequency of chromosome abnormalities than later ones. The incidence of trisomic abortions increases with maternal age, while the frequencies of polyploid and of 45,X abortions are independent of maternal age (Carr and Gedeon, 1977). Less than 1% of 45,X zygotes lead to 45,X liveborns. The generally accepted explanation for this is that 45,X zygotes are lethal but 45,X/46,XX and 45,X/46,XY mosaics are not, and liveborn 45,X individuals are presumed to have started out as mosaics, whether or not they still harbor some XX or XY cells.

Since monosomy may, in principle, arise through either chromosome loss or nondisjunction whereas trisomy results only from the latter process, monosomy should be more frequent among spontaneous abortuses than trisomy. Instead,

autosomal monosomy is almost nonexistent (Chapter 11). Monosomic zygotes presumably die so early that there is either no implantation (thus no recognized pregnancy) or no detectable products of conception to study.

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