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Chromosomal Disorders: Background and Neuroradiology

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Chromosomal aberrations, and their associated syndromes of dysmorphism and malformations of multiple organ systems, have been long recognized as significant causes of severe mental impairment. With a few major exceptions, these clinical syndromes have only recently been catalogued as systematically (1, 2) as have been single-gene disorders. The neuropathologic features of many of these syndromes have been characterized only broadly, if at all. Not surprisingly, there is no detailed compendium of the neuroradiologic features of the malformations of the central nervous system (CNS) associated with various chromosomal aberrations.

Certain chromosomal aberrations, such as trisomy 21 and the associated Down syndrome, are encountered with sufficient frequency to permit systematic study of their effects on the CNS. These studies show that disruption of the nervous system is nearly a universal feature of these syndromes, particularly those involving autosomes. Neuroradiologic investigations of these conditions are becoming increasingly important in their characterization for two reasons: 1) In some cases, admittedly few, CNS effects are mediated in part by surgically remediable structural abnormalities, such as hydrocephalus or atlantoaxial instability. These structural abnor-

malities can be detected by neuroimaging. 2) Most of the clinical syndromes associated with chromosomal abnormalities are notoriously variable, requiring individual assessment of each patient. Incompletely overlapping partial aneuploidies, for example, give rise to broadly similar syndromes, but slight differences in their extent may considerably alter the resultant phenotype. Neuroimaging can help to characterize the associated CNS pathology and facilitate proper management of the patient.

It is our purpose to introduce the chromosomal disorders to the general neuroradiologist by concentrating on basic concepts and by giving specific illustrations of some of the more commonly encountered syndromes. Limitations of space and of current knowledge preclude an encyclopedic treatment.

Genes and Chromosome Structure

The fundamental unit of inheritance is the gene, a linear array of DNA consisting of *exon* sequences encoding the structure of a single protein, noncoding *intron* sequences interspersed between the exons, and *regulatory regions* both upstream and downstream (3). It is estimated that the human genetic complement consists of 100,000 such genes, as well as other DNA sequences, some encoding transfer and ribosomal RNA, others with no known coding function. In humans, these genes are arranged like beads on 23 pairs of string-like chromosomes, in a characteristic order. Each chromosome is composed of a continuous DNA double helix, as well as associated histone and nonhistone (acidic) proteins. Of these 23 chromosome pairs, 22 pairs are autosomes that are represented equally in

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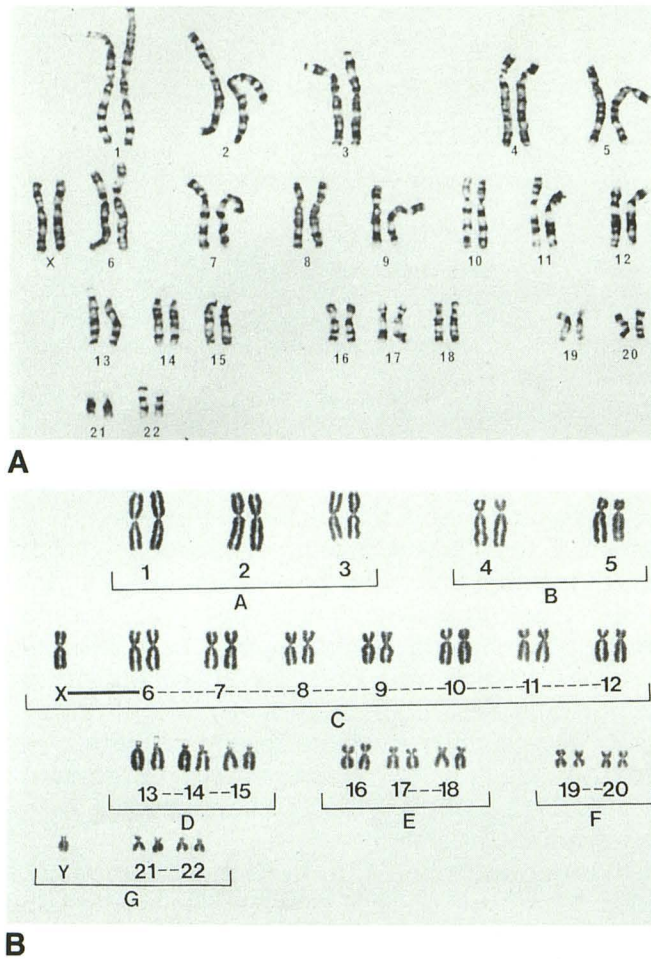


Fig. 1. Normal karyotypes. A, A normal female karyotype (46, XX). B, A normal male karyotype (46, XY).

both sexes, and one pair is the sex chromosomes, XX for the female (Fig. 1A) and XY for the male (Fig. 1B). A normal count of 23 pairs, ie, 46 chromosomes total, is known as the (2n) *diploid number*. A *haploid* number—one copy from each of the 23 pairs, (1n)—arises normally during meiosis, in the formation of eggs and sperm.

Genetic Diseases

Most genetic diseases can be considered to occur in three broad categories: Mendelian, polygenic, and chromosomal disorders. Each class has its own classification system and theory. The *Mendelian* disorders, named after the geneticist who described the theory underlying the inheritance of such traits, are the best understood of these diseases. Each of these diseases results from alteration at one gene locus. These disorders are most comprehensively catalogued in Mc-

Kusick's *Mendelian inheritance in man* (4). As of this writing, this continuously updated catalogue contains over 5000 entries.

Many human disorders—such as schizophrenia, hypertension, and diabetes—are thought to be *polygenic*, resulting from the summed effects of multiple genes dispersed widely on different chromosomes. Our understanding of such disorders in humans remains quite sketchy, although there is a well developed theory of such *Galtonian* transmission, that has been applied successfully by plant and animal breeders (5).

Chromosomal disorders, the topic of this paper, are defined by the presence of microscopically visible alterations in the number or structure of chromosomes. These diseases appear to result from the overrepresentation or underrepresentation of hundreds or thousands of contiguous genes. A useful compendium of these disorders is to be found in Schinzel's *Catalogue of unbalanced chromosome aberrations in man* (1).

Diagnosis of Chromosomal Disorders

Microscopic examination of the chromosomes is called *karyotype analysis*. Karyotype analysis can only detect gross structural alterations involving long stretches of chromosomes containing hundreds to thousands of genes. Karyotype analysis is not generally applicable to Mendelian or polygenic disorders, but it is useful to define the grosser chromosomal disorders. Karyotype analysis is performed clinically on preparations of chromosomes from peripheral blood lymphocytes or fibroblasts that have been arrested in the metaphase stage of the cell cycle. Such analysis can be performed on cells from amniotic fluid or from a chorionic villus biopsy for prenatal karyotyping. It can also be performed on tumor cells, which invariably have marked karyotypic abnormalities that distinguish them from the nonmalignant cells of the same individual. However, the chromosomal aberrations that we will be discussing usually affect every cell in a given individual—a different category of disorder.

Each human chromosome has a visible constriction called the *centromere* that separates its short arm (designated p) from its long arm (q). The size and position of the centromere are characteristic for each chromosome. Chromosomes are first identified by the size and position of the centromere and then subdivided further by their *banding patterns*. The banding pattern reflects differences in the staining intensity of each seg-

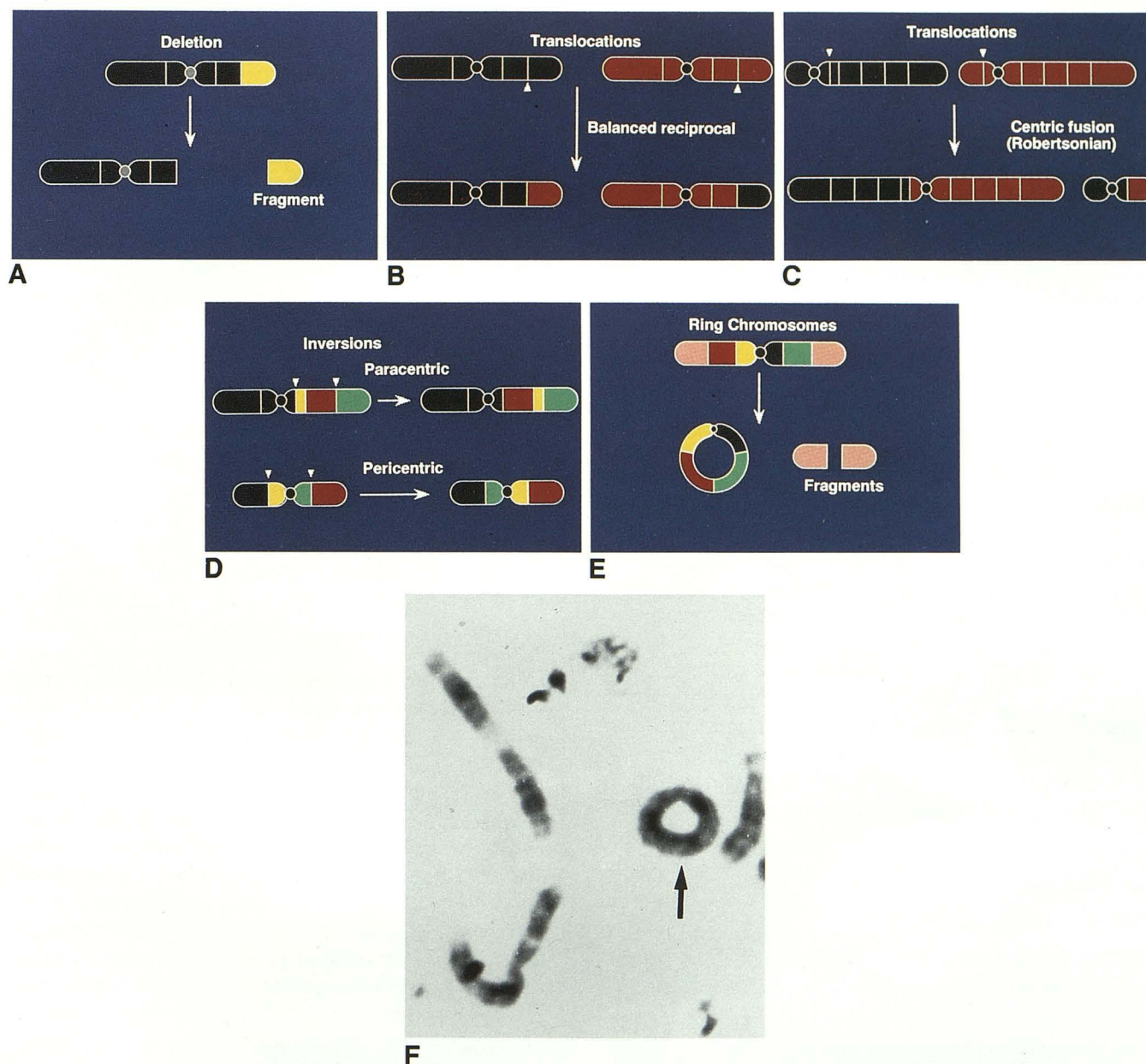


Fig. 2. Diagrammatic illustration of various structural abnormalities involving a chromosome (Reproduced with modification from Robbins et al (6), pp 126–125.) A, Deletion; B, balanced reciprocal translocation; C, Robertsonian translocation; D, inversions; E, ring chromosome; F, actual Ring chromosome (arrow). (Diagrammatic illustrations by Brent A. Bauer, MFA, of the Department of Art as Applied to Medicine of the Johns Hopkins School of Medicine.)

ment of the chromosome with any of a large variety of chromogenic or fluorescent dyes. Banding permits identification of those chromosomes or subchromosomal regions that may be altered in a given patient. However, even with the use of special techniques (eg, prometaphase banding, which allows examination of extended chromosomes that have not yet fully condensed into their metaphase configuration), karyology

has a limited resolution. Two chromosomes that appear to have identical deletions karyotypically may in fact differ by scores of genes.

Using karyotypes, the cytogeneticist can define several different types of disorder. *Euploidy* refers to the normal state of having a balanced set of chromosomes. *Aneuploidy* is a general term referring to any deviation from an exact multiple of the haploid number. Except in tumor cells or

spontaneous abortuses, the clinician usually encounters aneuploidy involving only a single chromosome—more extensive alterations being incompatible with life (Fig. 3). Such aneuploidy can be either an additional copy of a chromosome or one chromosome too few. For example, if autosome 18 is present in three copies rather than the expected two, this aneuploidy is referred to as *trisomy 18*; if chromosome 5 is present only in one copy rather than the expected two, then there is *monosomy 5*; if only a part of a chromosome is overrepresented or underrepresented, this is a *partial aneuploidy*.

Aneuploidy

Aneuploidy can result from loss (or gain) of an entire chromosome during cell division—an error known as nondisjunction—or from a structural abnormality. Structural abnormalities result from some form of chromosome breakage, with subsequent loss or rearrangement of material. Pathology then results from any of several mechanisms: 1) partial monosomy of a deleted subchromosomal region; 2) partial trisomy from a duplication; 3) interruption of the gene(s) through which the chromosomal breaks occurred; or, 4) more hypothetical positional effects, resulting from juxtaposition of structural genes into a novel regulatory region.

Partial Aneuploidies

Structural abnormalities recognized by cytogeneticists include deletions, duplications, inver-

sions, and translocations (Fig. 2A). A *terminal deletion* can occur when there is a single break in the arm of a chromosome. An *interstitial deletion* results when there are two breaks on a given chromosomal arm, with rejoining of the distal and proximal fragments. In either case, those chromosomal fragments that are no longer physically connected to a centromere are lost in the next cell division. One can specify in which region and at what band the break and deletion have occurred. For example, 46 XY, del(15) q11-q14 indicates a male individual with a normal total number of chromosomes but a deletion of bands 11 to 14 on the long (q) arm of one chromosome 15.

In translocation, a segment of one chromosome is transferred to another. In *balanced reciprocal translocation* (prevalence about 1 in 500 people), there are single breaks in each of the two chromosomes with exchange of material (Fig. 2B). In balanced translocation, there is no loss of genetic material (except, possibly, at the break points). The individual will be phenotypically normal. However, a balanced translocation carrier is at increased risk of producing abnormal gametes.

In the equally prevalent *Robertsonian translocation* (Fig. 2C), the breaks and reunion of two acrocentric chromosomes occur close to the centromere: in the long arm of one and in the short arm of the other. Transfer of the segments then leads to a metacentric chromosome and a small chromosome fragment. The small product is often lost, but it usually carries little genetic information. No unique genetic material is lost, so the phenotype is normal. However, metacen-

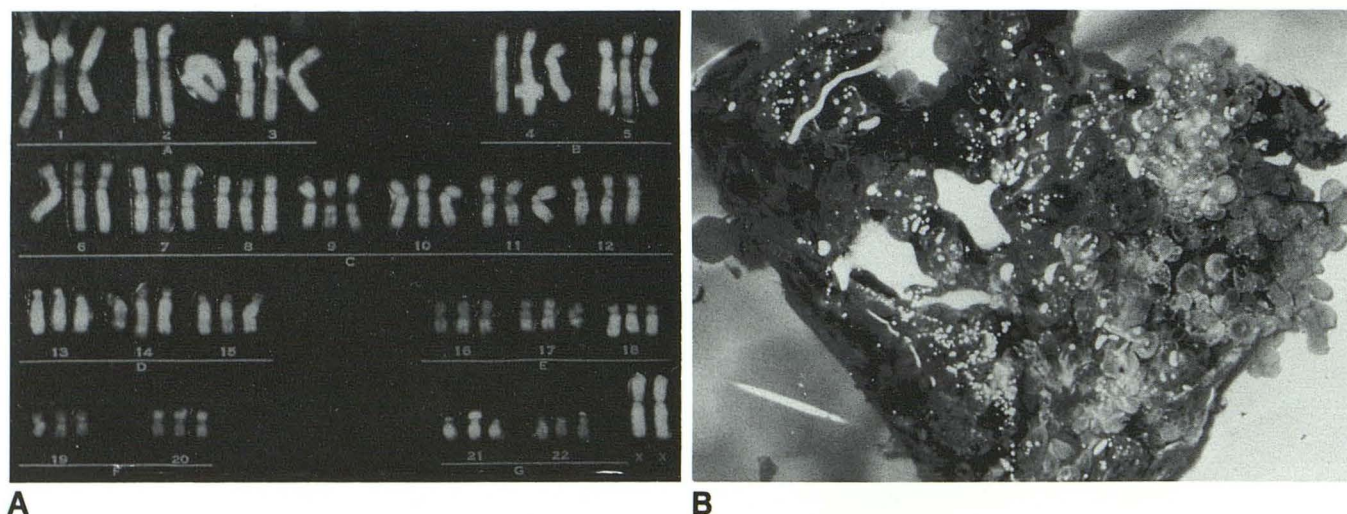


Fig. 3. Triploidy. A, Triploidy with three sets of each chromosome. B, Placenta in triploidy showing hydatidiform mole.

TABLE 1
Autosomal aberrations

A. Trisomies	
1.	Trisomy 21 (Down syndrome): incidence 1 in 1000 births
2.	Trisomy 18 (Edward syndrome): incidence 1 in 5000 births
3.	Trisomy 13 (Patau syndrome): incidence 1 in 6000 births
B. Partial autosomal aneuploidies	
1.	Deletion of the short arm of chromosome 4 (Wolfe syndrome)
2.	Deletion of the short arm of chromosome 5 (Cri Du Chat syndrome)
3.	Deletion on the long arm of chromosome 15 (Prader-Willi syndrome or Angelman syndrome)
4.	Deletion on the short arm of chromosome 17 (Miller-Dieker syndrome)
Sex chromosome abnormalities	
A. Sex chromosome increase syndromes	
1.	X chromosome: Klinefelter syndrome 47, XXY (1 in 1,000 male births)
2.	Y chromosome: 47, XYY (1 in 1,000 male births)
B. Sex chromosome decrease syndromes	
1.	X Chromosome: Turner syndrome 45, X (1 in 10,000 female births)
C. Fragile X syndrome: fragile site in the long arm of the X chromosome	

tric Robertsonian chromosome can segregate abnormally during meiosis; affected progeny may have unbalanced karyotypes as a result of inheriting the translocation chromosome in addition to the normal homolog from the other parent.

Inversion refers to a rearrangement that involves two breaks within a single chromosome with reincorporation of the inverted segment, thus transforming a sequence along the chromosome from ABCD to ACBD (Fig. 2D). Such an inversion involving only one arm of the chromosome is *paracentric*. An inversion in which breaks are on opposite sides of the centromere, with the inverted segment incorporating the centromere, are called *pericentric*. Unless a vital gene is interrupted at the break points, neither type of inversion involves loss or overrepresentation of genetic material, and would not have direct phenotypic consequences. However, inversion carriers are at increased risk of producing abnormal gametes, just like carriers of balanced translocations and Robertsonian translocations.

A *ring chromosome* (Figs. 2E and 2F) is produced when deletion occurs at both ends of a chromosome with fusion of the damaged ends. If significant genetic material is lost, phenotypic abnormalities result.

More Extensive Abnormalities

Abnormalities involving multiple chromosomes are usually lethal in utero. They have little

clinical interest to many physicians but concern the obstetrician as an important cause of failed pregnancies. Triploidy—the presence of three copies of each chromosome—is such an example (Fig. 3A). Triploidy occurs in 1%–2% of conceptions and is usually due to dispermy (fertilization of one egg by two sperm). It results in death in utero. In triploidy, the placenta usually shows changes of a hydatiform mole (Fig. 3B).

Summary

In summary, the chromosomal aberrations can be classified first according to whether they involve an autosome or a sex chromosome, second according to whether the chromosomal number has increased or decreased, and third according to the specific structural abnormality involving the chromosome (Table 1).

Autosomal Chromosomal Alterations

Most gross chromosomal alterations are not compatible with life, and are encountered only in spontaneous abortuses or in tumor cells. Indeed, such chromosomal alterations are believed to be causally related to such anomalies.

There are no complete autosomal *monosomies* compatible with life, except in a *mosaic* state (where only some cells are aneuploid, the remainder normal). The only complete *trisomies* that are compatible with extrauterine life are those of certain small autosomes: trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), and trisomy 13 (Patau syndrome). Therefore, with these exceptions, the only autosomal aberrations that one encounters clinically are 1) mosaic states for either trisomies or monosomies, in which only some cells in the body are affected; or 2) more commonly, partial monosomies or trisomies, in which only a portion of an autosome is misrepresented. There are hundreds—perhaps thousands—of these partial monosomies and trisomies, of which only a few are well-recognized clinical entities.

As a general rule, there are four cardinal clinical features of an autosomal aberration disorder: 1) intrauterine and postnatal growth retardation; 2) a pattern of dysmorphic features, usually involving the face, limbs, and genitalia; 3) malformations, usually involving multiple organ systems; and 4) severe dysfunction of the nervous system. Of these, the most consistent feature is usually severe impairment of the nervous system, most commonly manifested as significant mental re-

tardation. In most described autosomal aberration syndromes, neuroradiologic features have not been studied systematically.

Autosomal Trisomies

Trisomy 21 (Down Syndrome)

Described by Down in 1866, trisomy 21 is the most common chromosomal disorder and a lead-

ing cause of mental retardation. Eighty percent of the patients have an IQ of 25–50. In the United States, the incidence in newborns is about 1 in 1000. Maternal age plays an important role in the generation of trisomy 21. In children whose mothers are under age 20, the incidence is 1 in 1550. In those whose mothers are over age 45, the incidence is 1 in 25. This increased incidence is thought to result from an increasing frequency of nondisjunctive events with advancing maternal

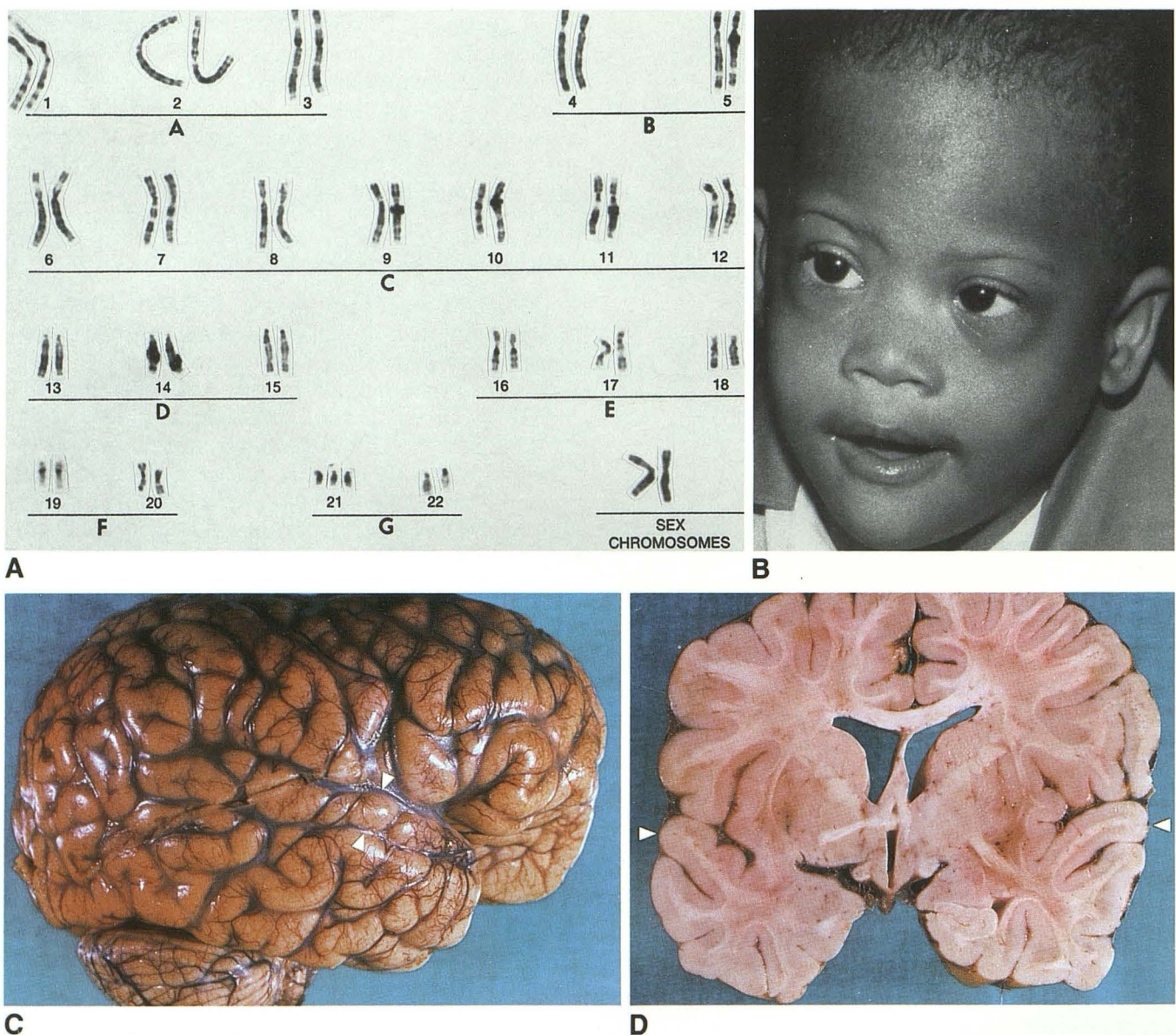


Fig. 4. Trisomy 21.

A, Karyotype indicating trisomy of chromosome 21.

B, Characteristic facies.

C, Gross brain of a 9-year-old girl with Down syndrome. Right lateral view demonstrates the typical small superior temporal gyrus (between white arrowheads) and rounded configurations of the brain.

D, Coronal section of C displays small superior temporal gyri (white arrowheads) bilaterally. In this patient, the insulae are well operculated.

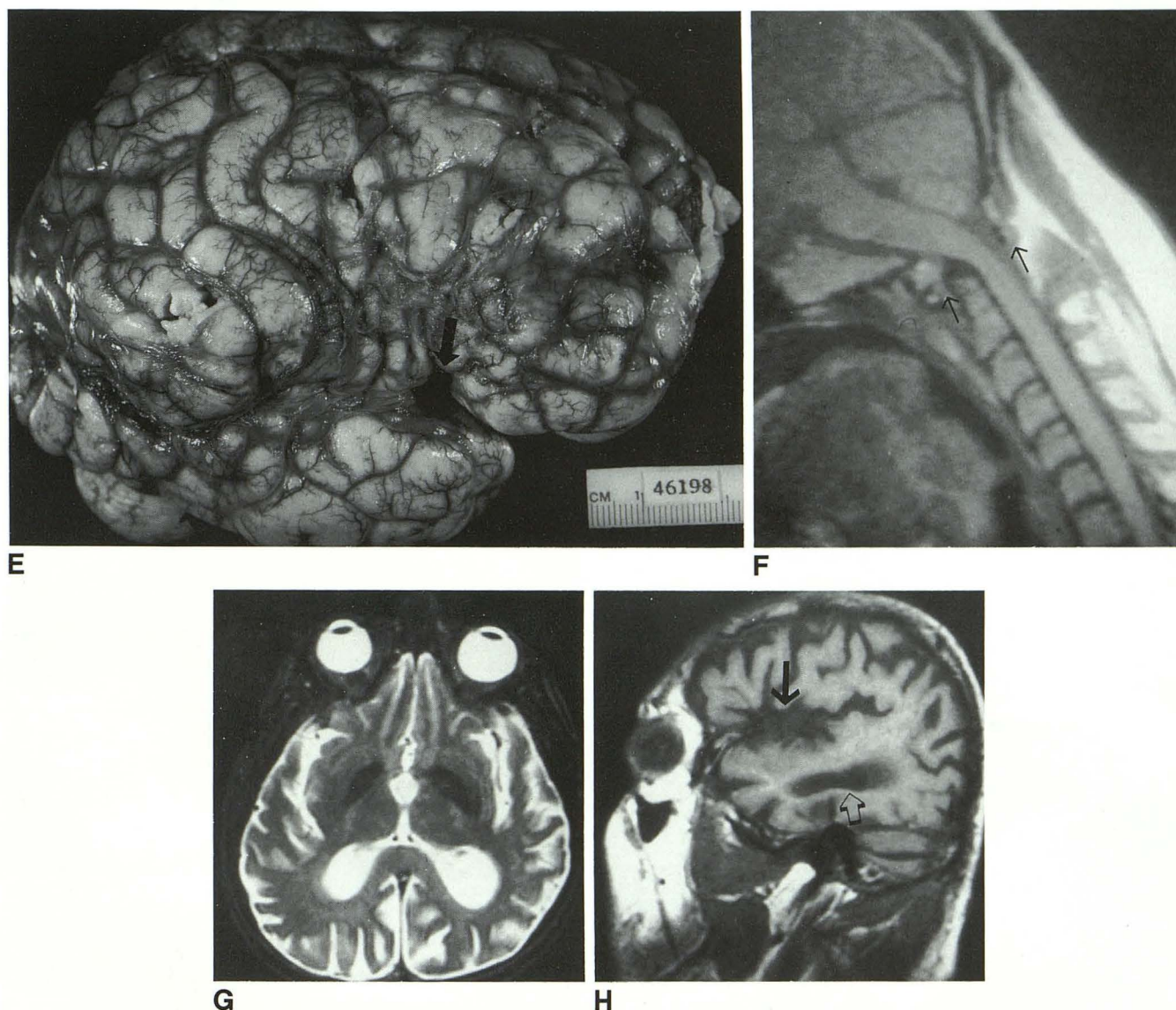


Fig. 4. —Continued.

E, Gross brain of a 2-year-old black girl with Down syndrome. Right lateral view demonstrates an open sylvian fissure (arrow) resulting from hypoplasia of the inferior frontal gyrus and the superior temporal gyrus.

F, Sagittal T1-weighted image of the cervical spine in a patient with Down syndrome demonstrating cord compression at C1, due to atlanto-axial dislocation (arrows) with abnormal forward angulation of the cervico-medullary junction.

G and *H*, 42-year-old man with Down syndrome. *G*, axial T2 MR shows moderate dilatation of the third ventricle and occipital horns with diffuse temporal lobe and occipital lobe atrophy. Note the short rounded contour of the skull and brain with narrow frontal lobes, a feature of Down syndrome. *H*, Parasagittal T1 MR reveals an enlarged temporal horn (open arrow) and an enlarged sylvian fissure (arrow) secondary to atrophy or under development of the inferior frontal gyrus and the superior temporal gyrus.

age. The same mechanism is thought to be a general phenomenon responsible for many aneuploidies. However, the precise mechanism of their generation remains obscure.

Several different abnormalities of chromosome 21 are associated with Down syndrome:

1. *Chromosome 21 trisomy*: This is the most common type (over 90%) (Fig. 4A);
2. *Down syndrome, translocation type*: About 4% of

Down syndrome results from this mechanism. In this type the total number of chromosomes is normal. However, the extra chromosomal material is either a de novo event or derives from the inheritance of a parental chromosome having a translocation of the long arm of chromosome 21 to another acrocentric chromosome, usually 22 or 14. Since the fertilized ovum already possesses two normal autosomes 21, the translocated material provides triplication of some of the genes, as occurs in trisomy 21. The translocated chromosome may be inherited from one

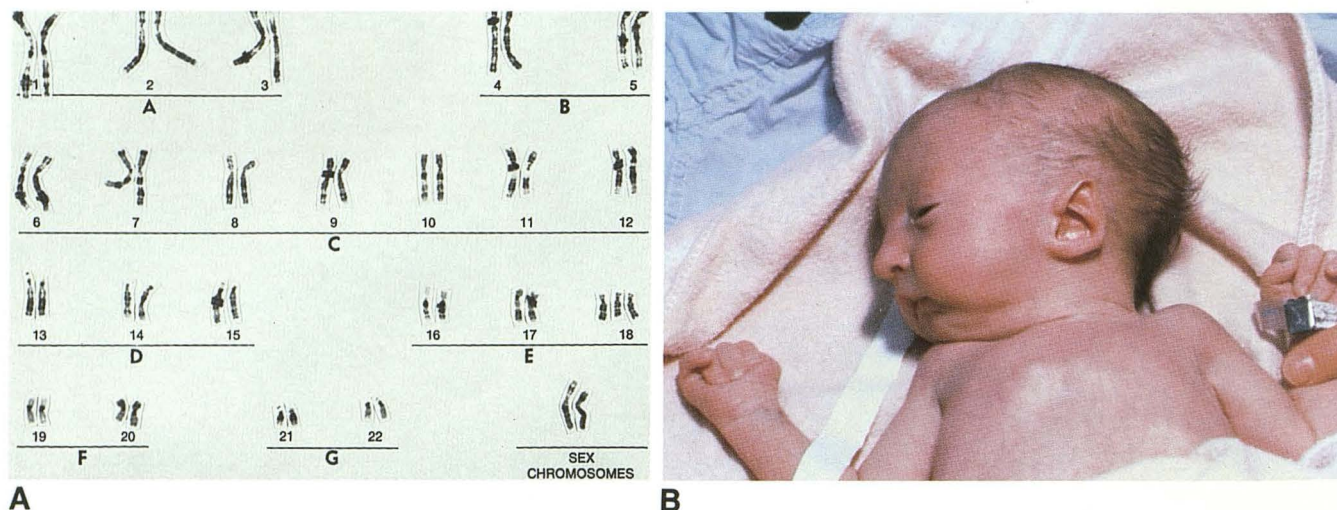


Fig. 5. Trisomy 18.

A, Karyotype indicating trisomy of chromosome 18.

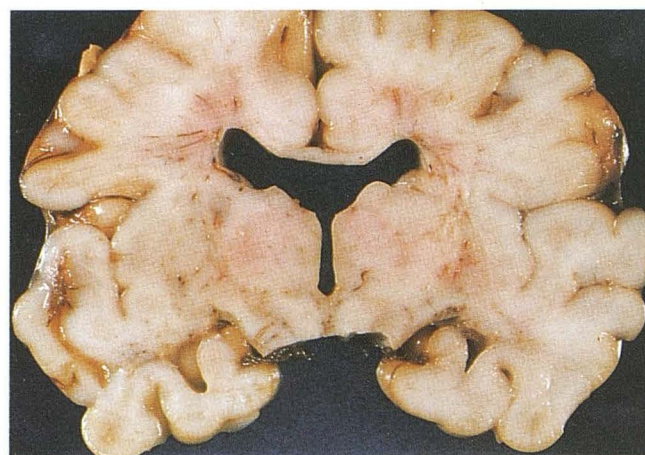
B, Neonatal photograph illustrates the dolichocephaly, low-set ears and micrognathia common in trisomy 17-18. The hands characteristically exhibit flexion and overriding of fingers bilaterally.

C, Coronal section of the brain displays poor delineation of the right superior, middle, and inferior temporal gyri and of the left inferior temporal gyrus. The fornices were situated far laterally with a wide cavum between. (Specimen courtesy Betty Ann Brody, MD.)

of the parents who is a carrier of a Robertsonian translocation (6). The symptoms of translocation Down syndrome are identical with those of the trisomy Down syndrome. In translocation Down syndrome, however, there is no effect of maternal age on the risk of recurrence;

3. *Down syndrome, mosaic type*: About 2%–3% of Down syndrome cases are mosaics having a mixture of cells with either 46 or 47 chromosomes. In mosaic Down syndrome, the symptoms are sometimes milder.

The facial features of trisomy 21 include brachycephaly; hypoplasia of the maxillae and nasal bones with flattening of the nasal bridge, orbital ridges, and maxillae; ocular hypotelorism; oblique palpebral fissures; epicanthal folds; spotting of the iris (Brushfield spots); cataracts; strabismus (one-third of patients); protruding fissured tongue with hypertrophied papillae; and small ears (Fig. 4B) (7).



Down syndrome is associated with multiple CNS abnormalities. These patients tend to develop Alzheimer disease at an early age, with senile plaques and neurofibrillary tangles ultrastructurally identical with those seen in typical cases of Alzheimer disease. When examined at autopsy, the brain is reduced in weight (rarely exceeding 1,000 g) and is abnormally round. A narrow superior temporal gyrus is a characteristic developmental abnormality observed in half the patients with Down syndrome (Figs. 4C and 4D). The insula is exposed because of hypoplasia of the inferior frontal gyrus (Fig. 4E).

Tamraz et al (8) have used magnetic resonance (MR) imaging to study the morphologic abnormalities of the skull, spine, brain, and spinal cord in Down syndrome. Skull abnormalities in Down syndrome include brachycephaly, short anterior segment of the skull base, increase in the angle of the base of the cranium, and delayed maturation.

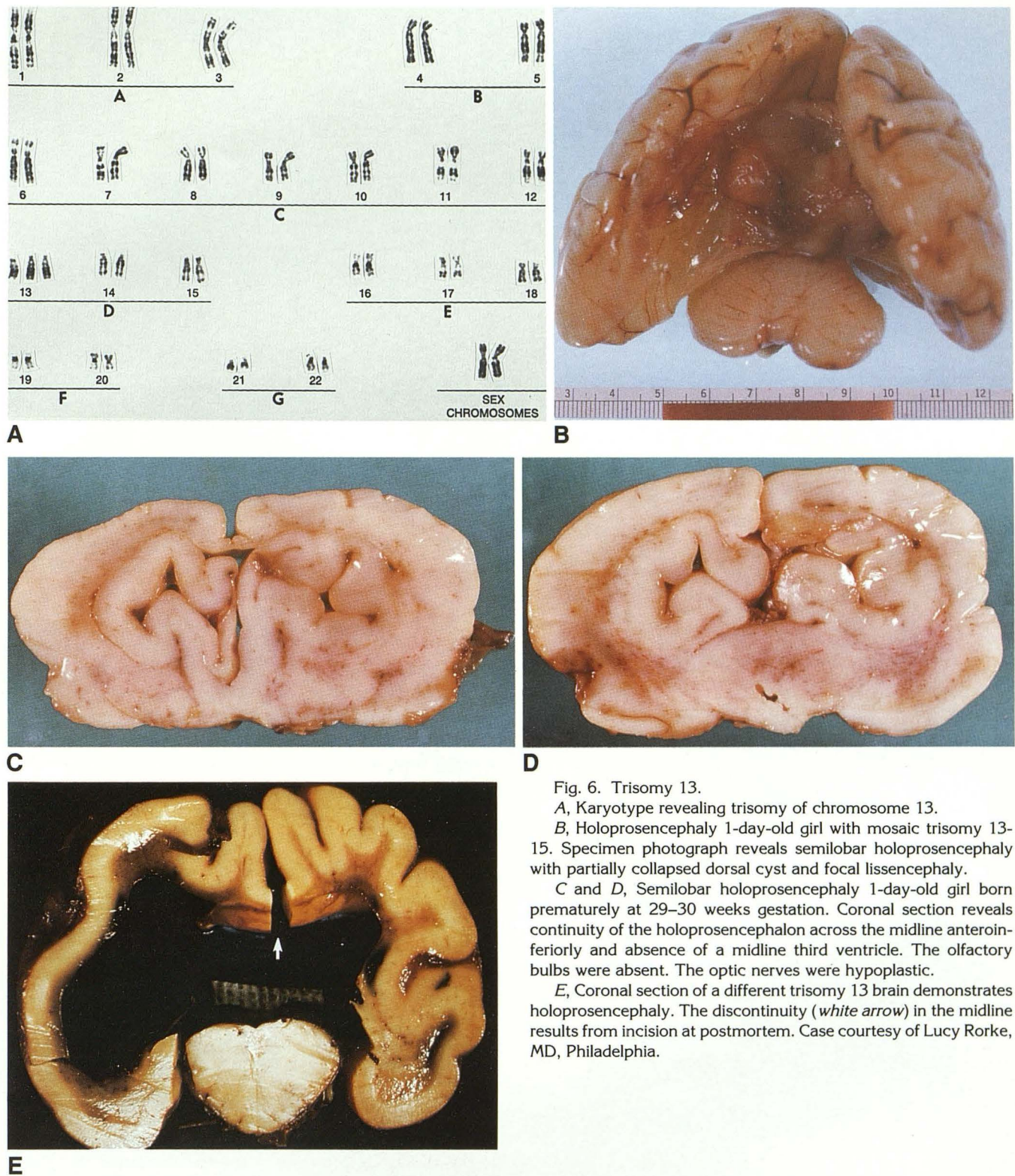


Fig. 6. Trisomy 13.

A, Karyotype revealing trisomy of chromosome 13.

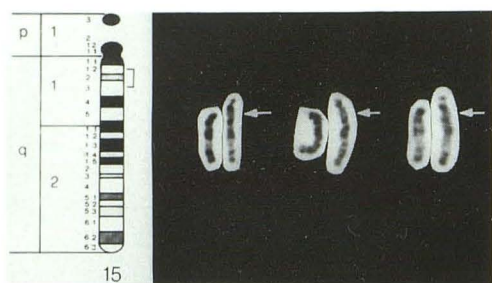
B, Holoprosencephaly 1-day-old girl with mosaic trisomy 13-15. Specimen photograph reveals semilobar holoprosencephaly with partially collapsed dorsal cyst and focal lissencephaly.

C and D, Semilobar holoprosencephaly 1-day-old girl born prematurely at 29–30 weeks gestation. Coronal section reveals continuity of the holoprosencephalon across the midline anteriorly and absence of a midline third ventricle. The olfactory bulbs were absent. The optic nerves were hypoplastic.

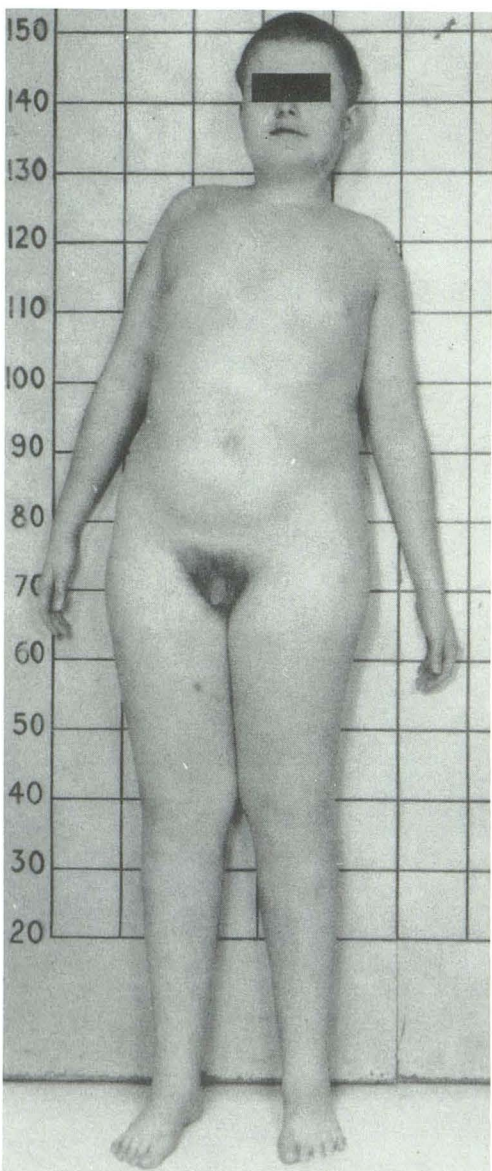
E, Coronal section of a different trisomy 13 brain demonstrates holoprosencephaly. The discontinuity (white arrow) in the midline results from incision at postmortem. Case courtesy of Lucy Rorke, MD, Philadelphia.

tion of the sphenoid bone. Cervical spine abnormalities include stenosis and atlanto-axial dislocation (12%–20%) resulting from ligamentous laxity (Fig. 4F). These important complications

are surgically correctable. Left uncorrected, however, they can result in compression of the upper cervical cord. More diffuse stenosis involving the thoracic and lumbar canal is also encountered.



A



B

Fig. 7. Prader-Willi syndrome.

A, Partial karyotype of Prader-Willi syndrome; the cytogenetic abnormality in Prader-Willi syndrome. An ideogram of chromosome 15 in prometaphase is illustrated on the left. Note the small bracket to the right of the ideogram; this delimits the interstitial deletion. Three pairs of chromosome 15 obtained from three



Fig. 8. Karyotype of Miller-Dieker syndrome demonstrating a terminal deletion (arrow) of the short arm of chromosome 17.

Neuroradiologically demonstrable brain abnormalities in Down syndrome (Figs. 4G and 4H) consist of a short and round brain, reduced anteroposterior diameter of the frontal lobes, a narrow superior temporal gyrus, small cerebellum, small pons, brain atrophy, and forward bending of the brain stem.

Trisomy 18 (Edwards Syndrome)

Described by Edwards in 1960, this is the second most commonly encountered trisomy syndrome in newborns. It may occur as a complete trisomy or as a mosaic form. Its incidence

separate lymphocytes arrested in prometaphase demonstrate the interstitial deletion found in the patient. The $\text{del}(15)(\text{q}11\text{q}13)$ chromosome is the one on the left in each pair. The arrows point to the normal chromosome 15 in each pair at the site of the interstitial deletion.

B, Photograph of a 29-year-old Prader-Willi man shows a height many standard below the adult mean and about average for a 12-year-old boy. There are small hands, small feet, and prominent truncal obesity.

(Reprinted with permission from Roberts (18).)

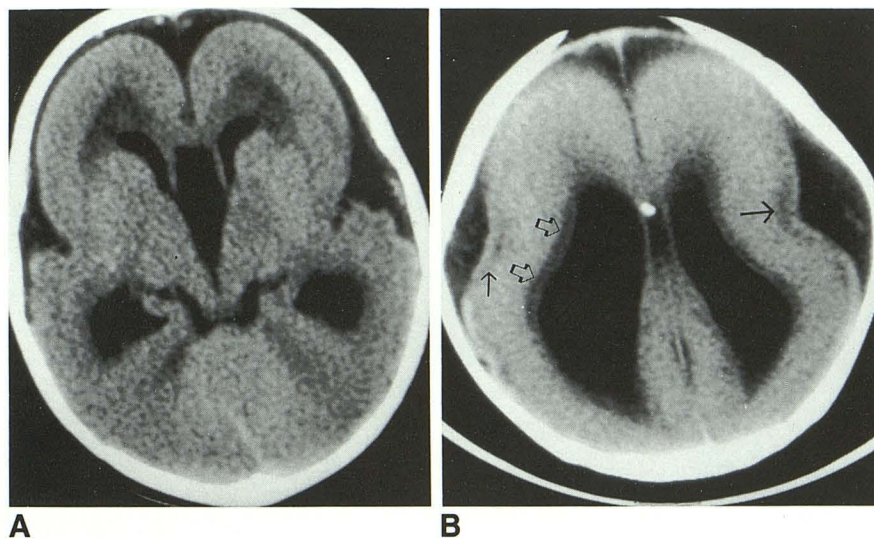


Fig. 9. *A* and *B*, Miller-Dieker syndrome. CT demonstrates the typical features of type 1 lissencephaly with open sylvian fissures giving the brain a "figure eight" configuration, smooth cortical surface, smooth sub-surface lines (*arrows*) representing an abnormal cortical layer, abnormal smooth white-gray interface (*open arrows*) without digitations, thickened cortex, thin white matter, high position of the third ventricle secondary to agenesis of the corpus callosum, enlargement of the lateral ventricles, and midline calcification.

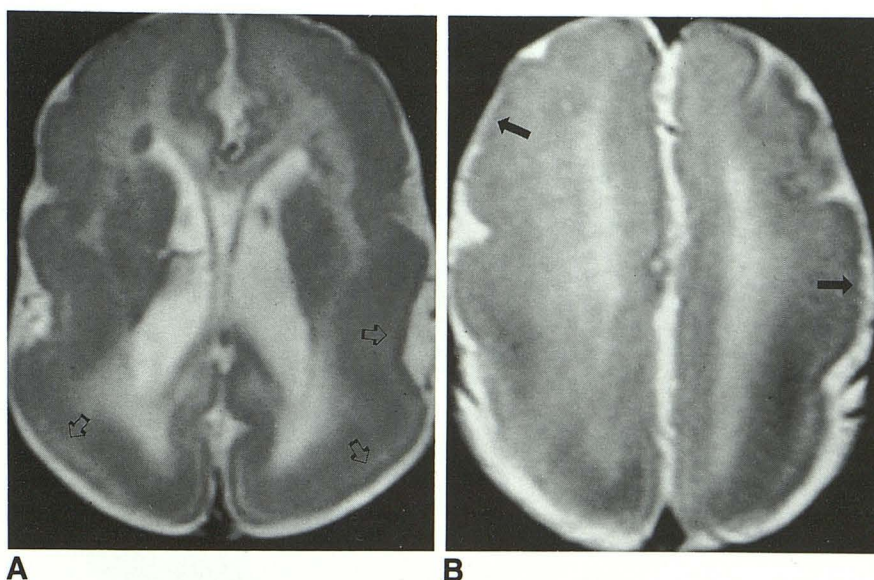


Fig. 10. *A* and *B*, Miller-Dieker syndrome. T2 MR shows pachygyria with a few broad flat gyri, thickened cortex, and thinned white matter. A rim of peripheral high intensity involving the outer cortex may represent the cell sparse layer (*open arrows* in *A*).

is 1 in 5,000 live births. Fewer than 10% of infants survive the first year. The patients exhibit dolichocephaly with prominent occiput; malformed low-set ears; micrognathia with small oral opening and short upper lip; cleft lip/cleft palate (one-sixth of cases); short palpebral fissures; epicanthal folds; ptosis of the eyelids; corneal opacities; and microphthalmos (Fig. 5B) (7, 9). The fingers flex and override such that the second finger often overlaps the third, and the fifth overlaps the fourth. Alternatively, the second finger may overlap the entire clenched fist (9). The most consistent neuropathologic findings are various anomalies in gyral and lobar patterns including dysplasia of the hippocampus, lateral geniculate

body and inferior olivary nuclei, and hypoplasia of the basis pontis. There are variations in the volume of the temporal, parietal, and occipital lobes and in the discernibility of specific gyri, including the superior temporal gyrus, gyrus rectus, precentral gyrus, and postcentral gyrus (Fig. 5C) (9, 10). The corpus callosum may be hypoplastic or absent. Heterotopias may coexist.

MR findings in trisomy 18 (8) consist of dolichocephaly, prominent occiput, narrow bifrontal diameter, hypertelorism, marked anteroposterior development of the temporo-occipital lobes, a mild form of holoprosencephaly, absence of the septum pellucidum, hypoplasia of the corpus callosum, and a small cerebellum.

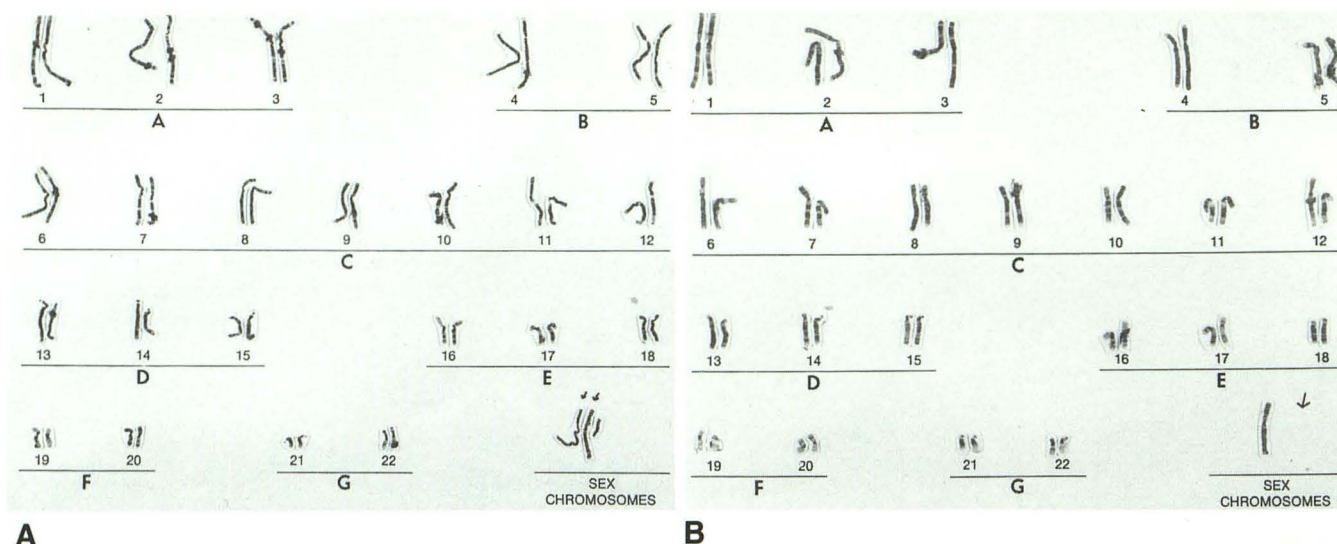


Fig. 11. Sex chromosome aberrations. A, Karyotype of Klinefelter syndrome (47, XXY). B, Karyotype of Turner syndrome 45, X.

Trisomy 13 (Patau Syndrome)

The trisomic etiology of this syndrome was discovered in 1960 by Patau et al (Fig. 6A). It may result from a complete trisomy, a Robertsonian translocation, or a mosaic form. Its incidence is about 1 in 6,000 live births. The expected life span is less than 9 months. The clinical features of trisomy 13 include multiple congenital anomalies such as microcephaly; severe mental retardation; absent eyebrows; shallow supraorbital ridges; epicanthal folds; major ocular anomalies, including anophthalmia, microphthalmia, and coloboma, micrognathia; cleft lip and cleft palate; malformed low-set ears; congenital heart disease; and brain anomalies (7).

Eighty percent of cases show characteristic holoprosencephaly with incomplete development of the forebrain, absence of the olfactory bulbs and tracts, and nondevelopment of the corpus callosum (Figs. 6B–6E). Cerebellar anomalies include dysplasia of the dentate nucleus and focal disorganization of the cerebellar cortex (10). MR findings in trisomy 13 (18) include microcephaly, holoprosencephaly, agenesis of the corpus callosum, Dandy-Walker variant, and hypoplasia of the inferior vermis.

Partial Autosomal Monosomies

Chromosome deletion syndromes involving virtually every chromosome have been identified with the new banding techniques. Deletion syndromes can involve either a short or long arm of

the chromosome. A few selected deletion syndromes are discussed.

Chromosome 4 (4p-, Deletion in the Short Arm; Wolf-Hirschhorn Syndrome)

These children have mental retardation and severe facial anomalies. In at least 1/3 of cases, death occurs during the first year of life, usually because of congestive heart failure from various cardiac defects. The oldest reported survivor was 24 years old. Brain malformations in the Wolf-Hirschhorn syndrome include midline defects, cerebellar anomalies, and disorders of gyration.

Chromosome 5: (5p-, Deletion in the Short Arm; Cri du Chat Syndrome)

This deletion syndrome is so named because affected children have a characteristic cry resembling that of a cat. The clinical features consist of microcephaly, hypertelorism, epicanthal folds, low-set ears, congenital heart disease, hypoplastic thumbs, very severe mental deficiency, and hypotonia.

Chromosome 15 (del(15)(q11q13); Prader-Willi Syndrome and the Angelman "Happy Puppet" Syndrome)

Deletions within bands q11 to q13 of chromosome 15 result in either of 2 distinct syndromes: the Angelman "Happy Puppet" syndrome—severe mental retardation, microcephaly, inappropriate laughter, and ataxia; or the Prader-Willi

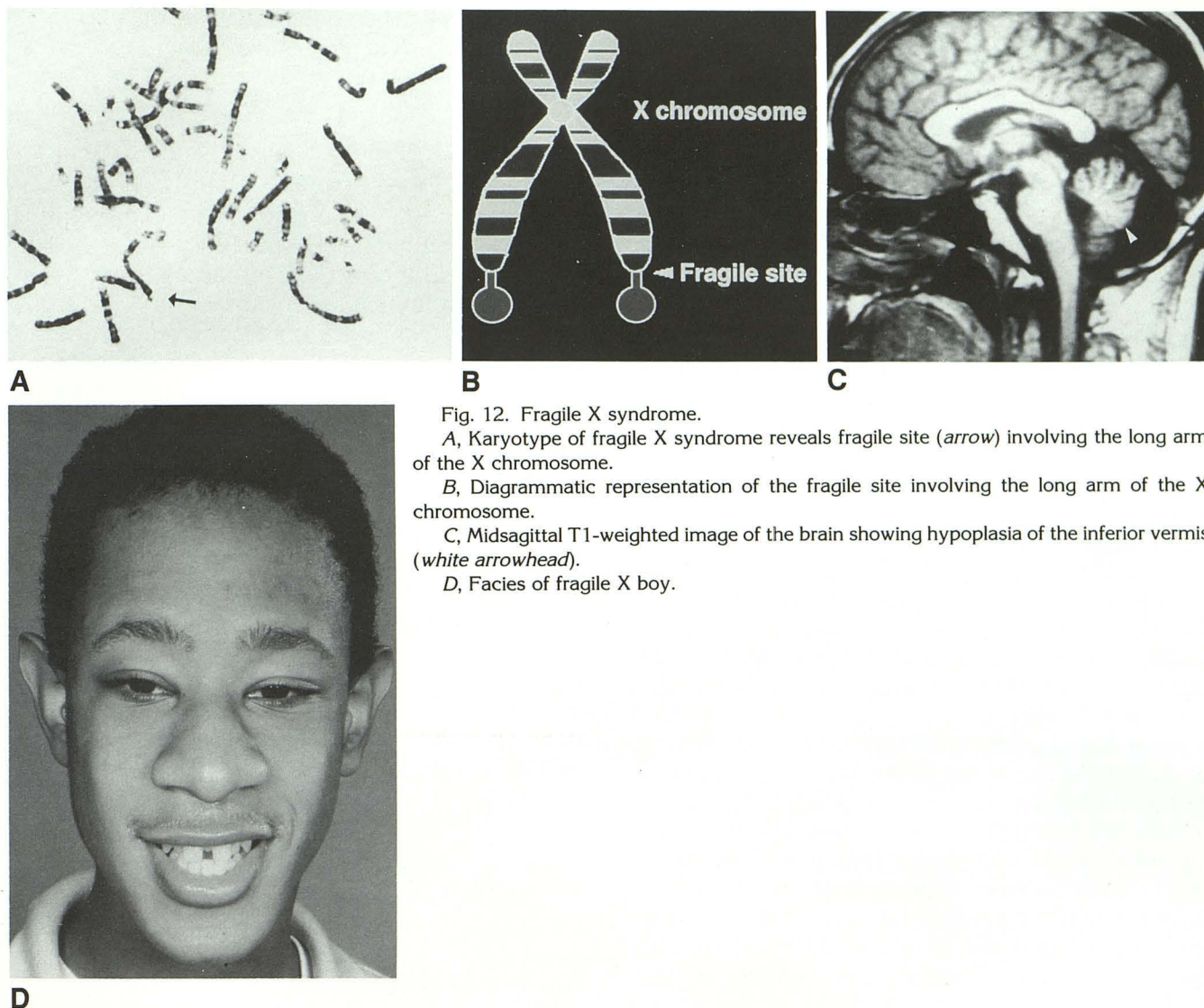


Fig. 12. Fragile X syndrome.

A, Karyotype of fragile X syndrome reveals fragile site (arrow) involving the long arm of the X chromosome.

B, Diagrammatic representation of the fragile site involving the long arm of the X chromosome.

C, Midsagittal T1-weighted image of the brain showing hypoplasia of the inferior vermis (white arrowhead).

D, Facies of fragile X boy.

syndrome (Fig. 7A)—mild to moderate mental retardation, obesity, short stature, and hypogonadism (Fig. 7B). The majority of cases of both syndromes are associated with similar—if not identical—deletions in the chromosomal region 15 q11-q13 (11). Although Angelman deletions are, on average, a bit larger than those associated with the Prader-Willi syndrome, comparison studies strongly suggest that it is not the size but the parental origin of the partial deletion that is the major determinant of the phenotype. In all informative cases of Angelman syndrome associated with deletions, these deletions were found to be of maternal origin. Thus, affected children had only paternal genes in this region. In contrast, in those Prader-Willi cases associated with deletions, these deletions were found to be of paternal origin. Furthermore, in studies of Prader-Willi patients that did not have grossly visible dele-

tions, some affected children were found to have maternal isodisomy for chromosome 15—two copies of the maternal chromosome, but no paternal copy (12). These studies strongly suggest that normal human development requires copies of genes from both parents.

Miller-Dieker Syndrome (Chromosome 17, Deletion of Short Arm) (Fig. 8)

Miller in 1963 and Dieker in 1969 identified a familial syndrome consisting of lissencephaly, multiple dysmorphic features, and a typical neurologic picture. Inheritance was thought to be autosomal recessive. Dobbins et al (13) found abnormalities of chromosome 17 consisting of a small terminal deletion in the short arm (p) in two patients who fit the criteria for Miller-Dieker syndrome. They proposed that partial monosomy of

distal 17p may be the cause for Miller-Dieker syndrome. Subsequent cases, including our own, support this association.

Clinical features of this malformation complex include ear anomalies; long, thin upper lip; anteverted nares; micrognathia; supernumerary digits; abnormal palmar creases; cardiac defects; cryptorchidism; and sacral dimple. Neurologic features include seizures, profound mental retardation, and marked hypotonia. Severe profound postnatal growth deficiency is also a feature of this syndrome.

The characteristic brain abnormality in Miller-Dieker syndrome consists of lissencephaly (a smooth cerebral surface with argyria and pachygyria); failure of opercularization of frontal and temporal lobes, leaving widely-open sylvian fissures; enlargement of ventricles in a nonobstructive pattern, especially posteriorly, similar to the fetal configuration called colpocephaly; absent or hypoplastic corpus callosum; and microcephaly. The cortex is abnormally thickened and, histologically, is divided into four layers instead of the usual six. The white matter is abnormally thin with heterotopic rests of gray matter scattered throughout. The usual white-to-gray matter ratio is reversed bringing the white-gray interface close to the ventricular surface (14) (Figs. 9 and 10).

Dobyns et al (15) have designated lissencephaly associated with Miller-Dieker syndrome as type I, whereas lissencephaly associated with obstructive hydrocephalus and with other brain malformations, such as hypoplasia of the vermis with or without Dandy-Walker malformation, is designated lissencephaly type II. They also have shown small midline calcifications in the septum pellucidum or genu of the corpus callosum by computed tomography (CT) in two patients with Miller-Dieker syndrome.

Sex Chromosome Aberrations

The clinical hallmark of most sex chromosome aberrations is infertility. In contrast to autosomal aberrations, growth retardation is not a prominent feature of individuals with abnormalities of the sex chromosomes. Indeed, individuals with a Y chromosome and supernumerary X chromosomes or with 2 Y chromosomes tend to be tall. Dysmorphism is quite mild. Major malformations are uncommon. Perhaps the most striking difference between autosomal and sex chromosomal abnormalities lies in their effects on the CNS. As a general rule, autosomal anomalies are associated with profound mental retardation, whereas

the mental and behavioral effects of sex chromosome disorders are either absent or, when present, considerably milder.

Klinefelter Syndrome (47, XXY Syndrome) (Fig. 11A)

This syndrome is one of the most frequent forms of genetic disease involving the sex chromosomes and the most common cause of hypogonadism in the male. Incidence is 1 in 1,000 male births. The extra chromosome is either of maternal or paternal origin. Advanced maternal age and irradiation are possible factors contributing to cause of this syndrome. Clinical features consist of testicular atrophy, azoospermia, small penis, lack of secondary male characteristics, female distribution of hair, gynecomastia, and increase in sole to os pubis length. Klinefelter syndrome is an important cause of sterility in the male. It is sometimes associated with a slight decrease in intelligence but most patients have an IQ in the normal range. Rare individuals with 48, XXXY or 49, XXXXY karyotypes have been identified. With an increasing number of X chromosomes, patients exhibit a greater degree of mental retardation.

Turner Syndrome 45, X (Fig. 11B)

Monosomy of the X chromosome in the absence of a Y chromosome is present in about 1:5000 newborns. Many more 45, X conceptuses die in utero, early in pregnancy. Turner syndrome usually arises sporadically.

Clinical features of the Turner syndrome include short stature, webbed neck, coarctation of the aorta, amenorrhea, and infertility. The syndrome is an important cause of infertility and short stature. There is no major dysfunction of the CNS. Average IQ of Turner patients is 95. Indeed, significant mental impairment in a Turner patient should prompt investigations for other disorders, such as additional chromosomal aberrations. The only neurologic dysfunctions consistently associated with 45, X syndrome are mild hearing impairment (present in about half of these patients) and bilateral ptosis, with or without strabismus (found in less than 20% of patients).

Fragile X Syndrome

The fragile X syndrome is recognized as an important genetic cause of neurodevelopmental disability in males and females. It is the second most commonly recognized genetic cause of

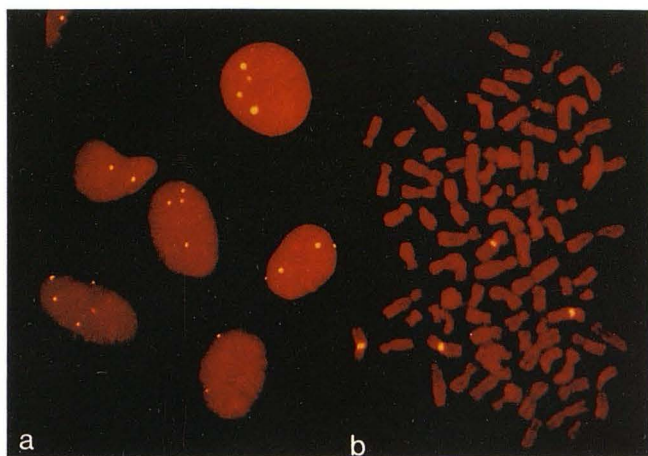
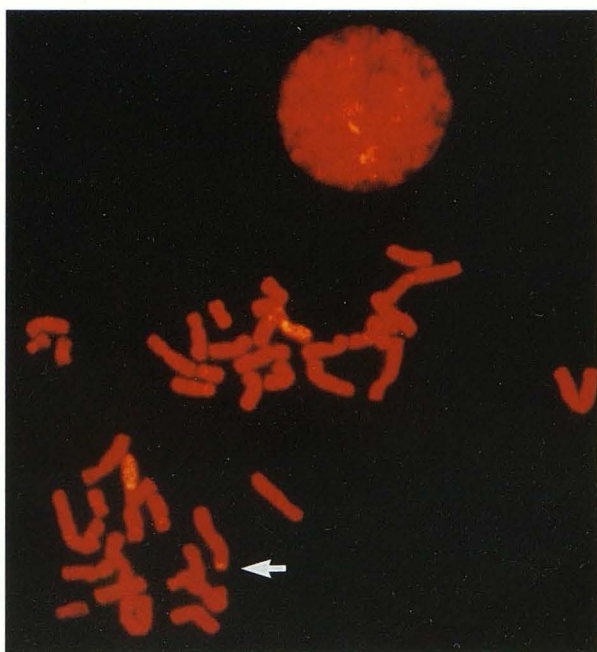


Fig. 13. In situ hybridization with a probe to the α satellite DNA of chromosome 7, marking chromosome 7 in interphase nuclei (A) and in metaphase chromosomes of a single cell (B). The position of the centromere of chromosome 7 is indicated by a bright yellow fluorescence. Both interphase nuclei and metaphase chromosomes can be scored to determine the number of copies of chromosome 7 in this cell line. In B, there are four centromeres of chromosome 7.

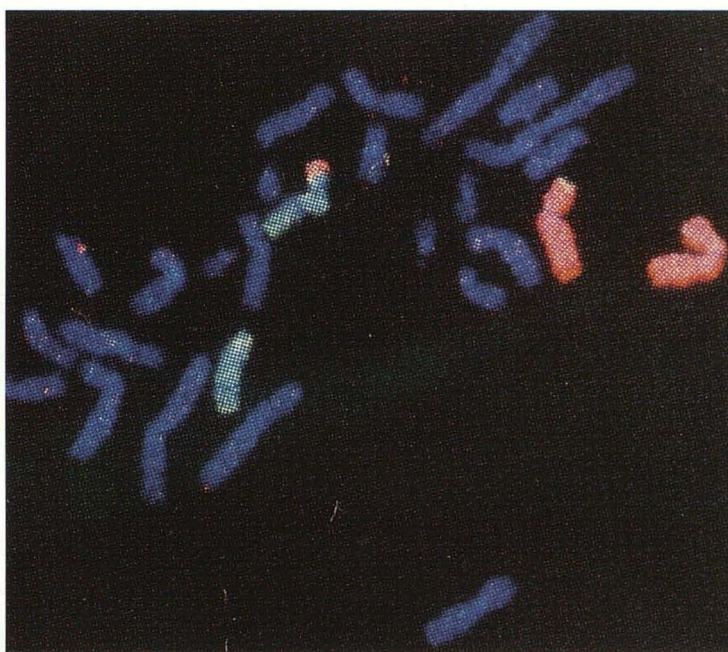
mental retardation in males, after Down syndrome. In this syndrome, the X chromosomes demonstrate a fragile site at band q27.3 (Fig. 12). The condition is transmitted through families as

an X-linked semidominant condition. Fragile X syndrome is associated with significant cognitive and behavioral disability in the majority of cytogenetically positive males. The IQ of fragile X males declines during childhood. The large majority of men with fragile X syndrome are mentally retarded in the moderate to severe range. However, fragile X boys fall in the mild to moderate range of mental retardation. A number of speech characteristics have been associated with fragile X syndrome, including rapid speech rhythm and speech impulsiveness. Other characteristics of the fragile X syndrome in males include hyperactivity, stereotypies, and social dysfunction. There is a specific pattern of behavioral abnormality consisting of high-frequency stereotypical motor behavior, such as hand-flapping and rocking; hypersensitivity to sound; repetitive smelling of non-food objects; gaze aversion, and self-injury.

Two-thirds of female carriers of the fragile X chromosome syndrome have normal or above average intelligence. About one-third of the females with fragile X syndrome are thought to have some degree of mental retardation. As would be expected, heterozygous females—carrying one normal and one fragile X chromo-



14



15

Fig. 14. Identification of chromosome 15 in a balanced translocation carrier by in situ hybridization with a fluorescent chromosome 15 DNA library probe. Note that there are two copies of chromosome 15 plus a very small part of chromosome 15 (white arrow) translocated to the terminal region of chromosome 3.

Fig. 15. Fluorescent in situ hybridization (FISH) used to "paint" chromosome 12 (green) and chromosome 7 (red). Note the reciprocal translocation. With this technique each chromosome can be identified by a different "paint" made from 10,000 to 100,000 fragments of DNA tagged with fluorescent dye and then hybridized to the chromosome. (Reprinted with permission from Roberts (18).)

TABLE 2
Index of Selected Malformations: Minor Anomalies of the CNS

Premature craniosynostosis occasional in	del(18p)
Trigonocephaly frequent in	dup(13) (q22 → qter)
Scalp defect occasional in	dup(13) (pter → q14)
Anencephalus occasional in	trisomy 18, trisomy 21
Arrhinencephaly frequent in	trisomy 13, triploidy
Absence or hypoplasia of the corpus callosum frequent in	trisomy 8 mosaicism, trisomy 18, triploidy
Fusion of thalami occasional in	dup(3) (q25 → qter)
Arnold-Chiari malformation occasional in	dup(3) (q25 → qter), dup(5p), trisomy 13, trisomy 18, triploidy, tetraploidy
Dandy-Walker malformation occasional in	dup(5p), dup(8) (pter → p21), triploidy
Cerebellar hypoplasia or dysplasia frequent in occasional in	dup(1) (q25 → qter) dup(3) (pter → p21), dup(3) (q21 → qter), del(4) (pter → p16.1), del(9) (pter → p21), dup(9p), dup(13) (q14 → qter)
Occipital or frontal encephalocele occasional in	dup(8) (q23 → qter), trisomy 18
Lumbar meningo-myelocele frequent in occasional in	triploidy dup(3) (q25 → qter), trisomy 18
Heterotopic neural cells frequent in	trisomy 13, trisomy 18
Congenital glaucoma frequent in occasional in	dup(3) (q25 → qter), del(11p13) trisomy 8 mosaicism
Coloboma of iris, choroid, retina frequent in	trisomy 13, triploidy
Microphthalmia, microcornea frequent in	dup(3) (q21 → qter), dup(4p), trisomy 9 mosaicism, triploidy
Agenesis of optic nerve occasional in	tetraploidy mosaicism
Retinoblastoma frequent in occasional in	del(13q14) (almost constant) trisomy 13, trisomy 21, especially in combination with sex chromosomal aneuploidy
Choanal atresia/stenosis occasional in	dup(4) (q31 → qter), dup(8) (q21 → qter), dup(10) (q21 → qter), triploidy, trisomy 18
Midface hypoplasia/hypoplasia of the maxilla frequent in	del(18) (q21 → qter)
Cleft lip and cleft palate frequent in	del(1), (q21 → q25), del(1) (q25 → q32), dup(3) (pter → p23), dup(3) (q21 → qter) & del(3) (pter → p25), del(4) (pter → p16.1), del(4) (q31 → qter), del(7) (q32 → qter), dup(9) (pter → q31), trip(9p), dup(10p), dup(11) (p14 → p12), dup(13) (q14 → qter), dup(22) (q13 → qter)
Atretic or stenotic external ear canals frequent in	del(18) (q21 → qter)

Note—Adapted and substantially abbreviated from Schinzel (1). Common dysmorphic features such as transverse palmar creases, inner epicanthic folds, hypertelorism, and some common malformations were not considered because of their frequent occurrence in a large number of aberrations. Frequent means present in at least 10% of reported cases. The abbreviation qter means the termination of the q arm of the chromosome. If one aberration is listed (eg, dup(13) (q32 → qter)), it is implied that the malformation/anomaly also occurs in all aberrations which include this segment (eg, in dup(13) (q14 → qter) or in trisomy 13).

some—are usually less cognitively affected than hemizygous males, who have only one X chromosome. Mentally retarded heterozygous females have been reported to demonstrate many of the behavioral patterns seen in hemizygous males, including hyperactivity and attention deficit, as well as stereotypical and autistic behavior.

Reiss et al (16, 17) have performed volumetric analysis of the cerebellar vermis from MR in 14 males and 12 females with the fragile X syndrome, comparing findings to those of age-matched subjects with other causes of develop-

mental disability or abnormal IQ. They found a significant decrease in the size of the posterior vermis and an increased fourth ventricular volume in fragile X patients. Reiss et al. (16, 17) speculate that the abnormalities represent hypoplasia of midline vermis, medial cerebellar hemispheres, and, perhaps, the brain stem (Fig. 12C) rather than atrophy. The posterior vermis receives tactile, auditory, and visual information. Through its connections with brain-stem reticular nuclei, the cerebellar vermis could play a role in modulating attention as well.

Future Directions

New methods of identifying specific regions of the chromosome now provide a powerful tool for identifying specific alterations along the chromosome. Nonradioactive fluorescent probes can be hybridized directly to specific segments of DNA within the chromosomes and then detected by their fluorescence. This technique makes it possible to label specific chromosomes in both metaphase spreads and interphase nuclei. Whole chromosomes can be labeled individually with DNA libraries prepared from fluorescence-activated cell-sorted chromosomes. Alternatively, specific centromeres can be labeled with satellite DNA. Pieces of DNA as small as 1 kilobase can be mapped directly onto chromosomes with this method. Figure 13 shows an α satellite probe (D7Z1 from Oncor, Inc) which marks chromosome 7 in a transformed human-cell line. Figure 14 shows a chromosome 15 DNA library (pBS15 from J. W. Gray Lawrence Livermore Laboratories) used to detect this chromosome in a cell from a chromosome translocation carrier. Figure 15 shows "painting" of specific chromosomes by fluorescent in situ hybridization (FISH) to demonstrate their number and a reciprocal translocation (18). These new methods will enhance the resolution of cytogenetics and make it possible to evaluate the sex chromosomes and some cytogenetic abnormalities (eg, monosomy, trisomy, triploidy, mosaicism) directly in interphase nuclei. New work suggests that it may soon be possible to harvest fetal cells from the *maternal* circulation, concentrate them by flow cytometry, and then use the FISH techniques to identify fetal chromosomal abnormalities by maternal blood sampling. If successful, this technique could eliminate the need for amniocentesis or chorionic villus sampling to test fetuses for chromosomal anomalies.

In addition to the commonly recognized syndromes described above, there is a large variety of other conditions that may be encountered by the neuroradiologist. Some of these chromosomal aberrations will give rise to prominent anatomic abnormalities. Table 2, modified from Schinzel's catalogue (1), lists some of the anomalies commonly encountered in such syndromes. None of these anomalies is pathognomonic of a given chromosomal aberration, nor, for the most part, is any anomaly invariably present in all patients who have a given chromosomal aberration. However, recognition of such associations will occasionally permit the neuroradiologist to alert the

clinician and the karyologist to a potential chromosomal aberration. Such notification will be particularly useful for the detection of partial chromosomal aneuploidies, which can easily be missed by routine karyotyping. Alerting the karyologist to be mindful of a potential problem in a particular chromosomal region will permit application of the newer, specialized banding or molecular techniques appropriate to that region (Figs. 13–15), permitting diagnoses that might otherwise be missed.

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