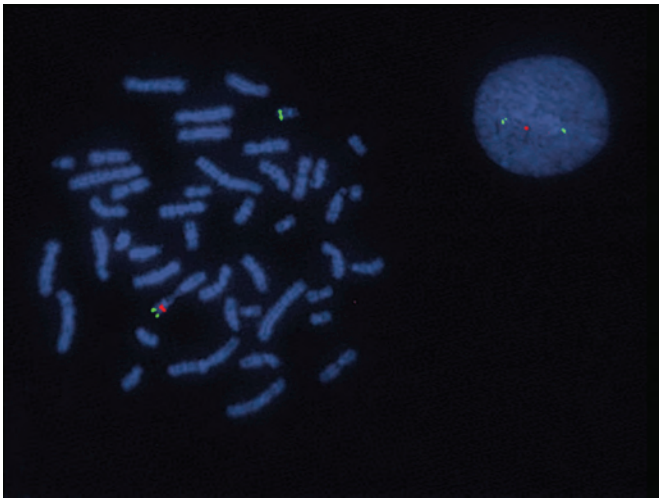

Figure 5-21 Fluorescence in situ hybridization of both metaphase chromosomes and an interphase cell from a patient with DiGeorge syndrome demonstrating the deletion of a probe that maps to chromosome 22q11.2. The 22q11.2 probe is in red, and the control probe, localized to 22q, is in green. The metaphase spread shows one chromosome 22 with both a green signal (control probe) and a red signal (from the 22q11.2 probe). The other chromosome 22 shows only hybridization with the control probe (green), but no red 22q11.2 signal since there is a deletion on this chromosome. The interphase cell also shows a hybridization pattern consistent with a deletion of chromosome 22q11.2. (Courtesy of Dr. Stuart Schwartz, Department of Pathology, University of Chicago, Chicago, IL.)

of the deletion by FISH (Fig. 5-21). By this test, approximately 90% of those previously diagnosed as having DiGeorge syndrome and 80% of those with the velocardiofacial syndrome have a deletion of 22q11.2. Thirty percent of individuals with conotruncal cardiac defects but no other features of this syndrome also reveal deletions of the same chromosomal region.

The molecular basis of this syndrome is not fully understood. The deleted region is large (approximately 1.5 megabases) and includes many genes. The clinical heterogeneity, with predominant immunodeficiency in some cases (DiGeorge syndrome) and predominant dysmorphology and cardiac malformations in other cases, probably reflects the variable position and size of the deleted segment from this genetic region. Approximately 30 candidate genes have been mapped to the deleted region. Among these, *TBX1,* a T-box transcription factor is most closely associated with the phenotypic features of this syndrome. This gene is expressed in the pharyngeal mesenchyme and endodermal pouch from which facial structures, thymus, and parathyroid are derived. The targets of *TBX1* include *PAX9,* a gene that controls the development of the palate, parathyroids, and thymus. Clearly there are other genes that contribute to the behavioral and psychiatric disorders that remain to be identified.

KEY CONCEPTS

Cytogenetic Disorders Involving Autosomes

- **Down syndrome** is associated with an extra copy of genes on chromosome 21, most commonly due to trisomy 21 and less frequently from translocation of extra chromosomal material from chromosome 21 to other chromosomes or from mosaicism.
- Patients with Down syndrome have severe mental retardation, flat facial profile, epicanthic folds, cardiac malformations, higher risk of leukemia and infections, and premature development of Alzheimer disease.
- Deletion of genes at chromosomal locus 22q11.2 gives rise to malformations affecting the face, heart, thymus, and parathyroids. The resulting disorders are recognized as
  - **DiGeorge syndrome** (thymic hypoplasia with diminished T-cell immunity and parathyroid hypoplasia with hypocalcemia) and
  - **Velocardiofacial** syndrome (congenital heart disease involving outflow tracts, facial dysmorphism, and developmental delay).

Cytogenetic Disorders Involving Sex Chromosomes

Genetic diseases associated with changes involving the sex chromosomes are far more common than those related to autosomal aberrations. Furthermore, imbalances (excess or loss) of sex chromosomes are much better tolerated than are similar imbalances of autosomes. In large part, this latitude relates to two factors that are peculiar to the sex chromosomes: (1) lyonization or inactivation of all but one X chromosome and (2) the modest amount of genetic material carried by the Y chromosome. These features are discussed briefly in relation to sex chromosomal disorders.

In 1961, Lyon outlined the idea of X-inactivation, now commonly known as the Lyon hypothesis. It states that *(1) only one of the X chromosomes is genetically active, (2) the other X of either maternal or paternal origin undergoes heteropyknosis and is rendered inactive, (3) inactivation of either the maternal or paternal X occurs at random among all the cells of the blastocyst on or about day 5.5 of embryonic life, and (4) inactivation of the same X chromosome persists in all the cells derived from each precursor cell.* Thus, the great preponderance of normal females are in reality mosaics and have two populations of cells, one with an inactivated maternal X and the other with an inactivated paternal X. Herein lies the explanation of why females have the same dosage of X-linked active genes as have males. The inactive X can be seen in the interphase nucleus as a darkly staining small mass in contact with the nuclear membrane known as the Barr body, or X chromatin. The molecular basis of X inactivation involves a unique gene called *XIST,* whose product is a long noncoding RNA (Chapter 1) that is retained in the nucleus, where it "coats" the X chromosome that it is transcribed from and initiates a gene-silencing process by chromatin modification and DNA methylation. The *XIST* allele is switched off in the active X.

Although it was initially thought that all the genes on the inactive X are "switched off," more recent studies have revealed that many genes escape X inactivation. Molecular studies suggest that 21% of genes on Xp, and a smaller number (3%) on Xq escape X inactivation. At least some of the genes that are expressed from both X chromosomes are important for normal growth and development. This notion is supported by the fact that patients with monosomy of