Expert CONSULT

Nelson Textbook of PEDIATRICS
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Down Syndrome

Trisomy 21 is the most common genetic cause of moderate mental retardation. The incidence of Down syndrome in live births is approximately 1 in 733; the incidence at conception is more than twice that rate; the difference is accounted by early pregnancy losses. In addition to cognitive impairment, Down syndrome is associated with congenital anomalies and characteristic dysmorphic features (Figs. 76-8 and 76-9; Table 76-3). Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of trisomy 21. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects, ventricular septal defects, isolated secundum atrial septal defects, patent ductus arteriosus, and tetralogy of Fallot. Congenital and acquired gastrointestinal anomalies and hypothyroidism are common (Table 76-4). Other abnormalities include megakaryoblastic leukemia, immune dysfunction, diabetes mellitus, and problems with hearing and vision (see Table 76-4). Alzheimer disease–like dementia is a known complication that occurs as early as the 4th decade and has an incidence 2-3 times higher than sporadic Alzheimer disease. Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies. Two genes (*DYRK1A, DSCR1*) in the putative critical region of chromosome 21 may be targets for therapy.

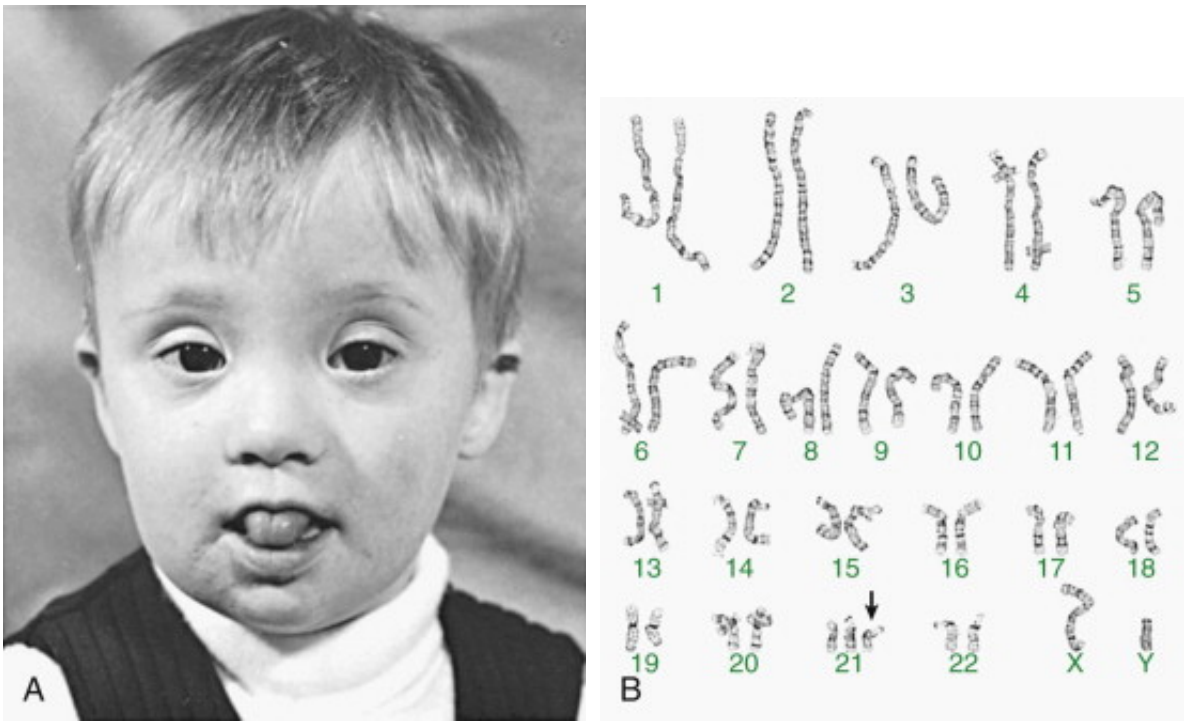

Figure 76-8 *A,* Face of a child with Down syndrome. *B,* Karyotype of a male with trisomy 21 as seen in Down syndrome. This karyotype reveals 47 chromosomes instead of 46, with an extra chromosome in pair 21.

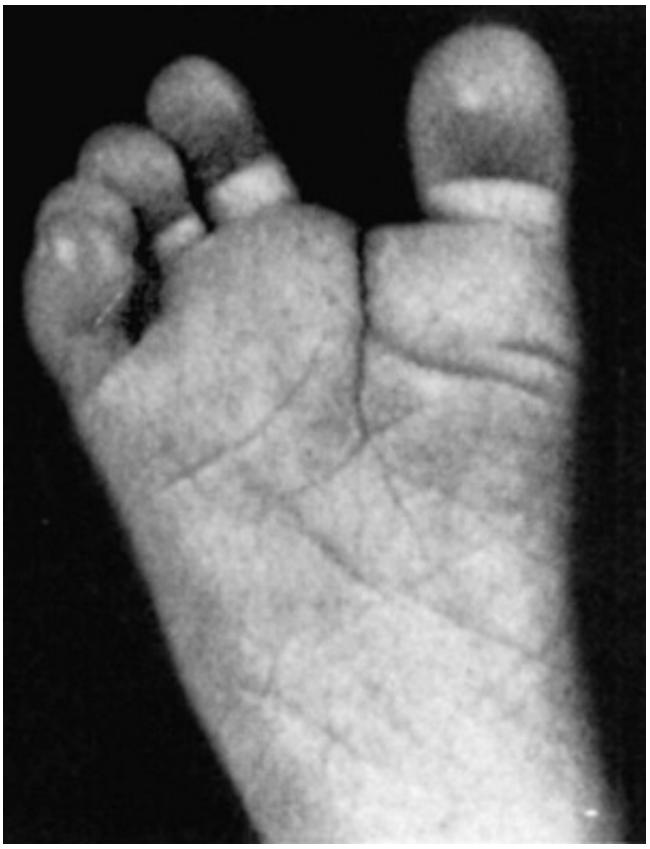

Figure 76-9 Prehensile foot in a 1-mo-old child.
(From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St Louis, 1989, Mosby.)

Table 76-3 -- CLINICAL FEATURES OF DOWN SYNDROME IN THE NEONATAL PERIOD

CENTRAL NERVOUS SYSTEM
Hypotonia*
Developmental delay
Poor Moro reflex*
CRANIOFACIAL
Brachycephaly with flat occiput
Flat face*
Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short hard palate
Small nose, flat nasal bridge

Protruding tongue, open mouth
Small dysplastic ears*
CARDIOVASCULAR
Endocardial Cushing defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension
MUSCULOSKELETAL
Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short 5th digit with clinodactyly*
Single transverse palmar creases*
Wide gap between 1st and 2nd toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers
GASTROINTESTINAL
Duodenal atresia
Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus
CUTANEOUS
Cutis marmorta

* Hall's criteria to aid in diagnosis.

Table 76-4 -- ADDITIONAL FEATURES OF DOWN SYNDROME THAT CAN DEVELOP OR BECOME SYMPTOMATIC WITH TIME

NEUROPSYCHIATRIC
Developmental delay
Seizures
Autism spectrum disorders
Behavioral disorders (disruptive)
Depression
Alzheimer disease
SENSORY
Congenital or acquired hearing loss
Serous otitis media
Refractive errors (myopia)

Congenital or acquired cataracts
Nystagmus
Strabismus
Glaucoma
Blocked tear ducts
CARDIOVASCULAR
Acquired mitral, tricuspid, or aortic valve regurgitation
Endocarditis
MUSCULOSKELETAL
Atlantoaxial instability
Hip dysplasia
Slipped capital femoral epiphyses
Avascular hip necrosis
Recurrent joint dislocations (shoulder, knee, elbow, thumb)
ENDOCRINE
Congenital or acquired hypothyroidism
Diabetes mellitus
Infertility
Obesity
Hyperthyroidism
HEMATOLOGIC
Transient lymphoproliferative syndrome
Acute lymphocytic leukemia
Acute myelogenous leukemia
GASTROINTESTINAL
Celiac disease
Delayed tooth eruption
Respiratory
Obstructed sleep apnea
Frequent infections (sinusitis, nasopharyngitis, pneumonia)
CUTANEOUS
Hyperkeratosis
Seborrhea
Xerosis
Perigenital folliculitis

Developmental delay is universal (Tables 76-5 and 76-6; Fig. 76-10). Cognitive impairment does not uniformly affect all areas of development. Social development is relatively spared, but children with Down syndrome have considerable difficulty using expressive language. Understanding these individual developmental strengths will maximize the educational process for children with Down syndrome. Persons with Down syndrome often benefit from programs aimed at stimulation, development, and education. These programs are most effective in addressing social skills that often appear advanced for the intellectual delay. Children with Down syndrome also benefit from anticipatory guidance, which establishes the protocol for screening, evaluation, and care for patients with genetic syndromes and chronic disorders

(Table 76-7).

Table 76-5 -- DEVELOPMENTAL MILESTONES

MILESTONE	CHILDREN WITH DOWN SYNDROME		UNAFFECTED CHILDREN	
	Average (mo)	Range (mo)	Average (mo)	Range (mo)
Smiling	2	1½–3	1	½–3
Rolling over	6	2-12	5	2-10
Sitting	9	6-18	7	5-9
Crawling	11	7-21	8	6-11
Creeping	13	8-25	10	7-13
Standing	10	10-32	11	8-16
Walking	20	12-45	13	8-18
Talking, words	14	9-30	10	6-14
Talking, sentences	24	18-46	21	14-32

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, ed 2, Philadelphia, 1992, Saunders.

Table 76-6 -- SELF-HELP SKILLS

SKILL	DOWN SYNDROME CHILDREN		UNAFFECTED CHILDREN	
	Average (mo)	Range (mo)	Average (mo)	Range (mo)
EATING				
Finger feeding	12	8-28	8	6-16
Using spoon/fork	20	12-40	13	8-20
TOILET TRAINING				
Bladder	48	20-95	32	18-60
Bowel	42	28-90	29	16-48
DRESSING				
Undressing	40	29-72	32	22-42
Putting clothes on	58	38-98	47	34-58

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, ed 2, Philadelphia, 1992, Saunders.

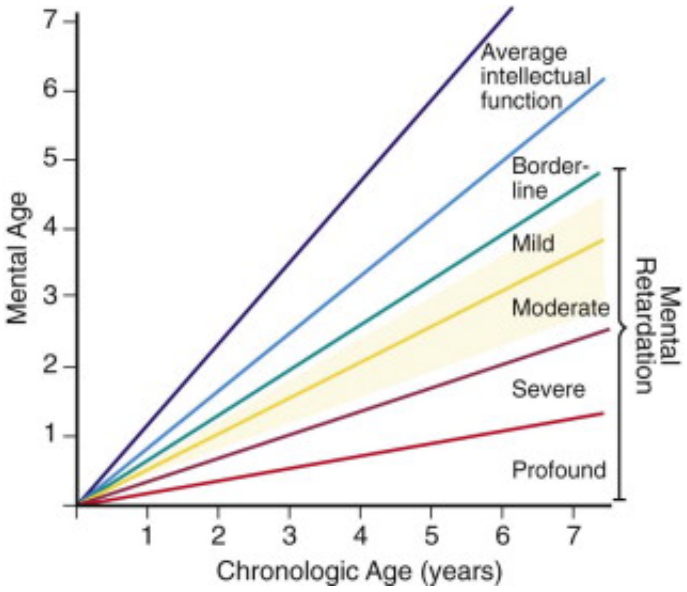

Figure 76-10 The area shaded in yellow denotes the range of intellectual function of the majority of children with Down syndrome. *(From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, ed 2, Philadelphia, 1992, WB Saunders, p 226.)*

Table 76-7 -- HEALTH SUPERVISION FOR CHILDREN WITH DOWN SYNDROME

CONDITION	TIME TO SCREEN	COMMENT
Congenital heart disease	Birth; by pediatric cardiologist Young adult for acquired valve disease	50% risk of congenital heart disease. Increased risk for pulmonary hypertension
Strabismus, cataracts, nystagmus	Birth or by 6 mo; by pediatric ophthalmologist **Check vision annually**	Cataracts occur in 15%, refractive errors in 50%
Hearing impairment or loss	Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing; check hearing q6mo up to 3 yrs if tympanic membrane is not visualized; **annually thereafter**	Risk for congenital hearing loss plus 50-70% risk of serous otitis media.
Constipation	Birth	Increased risk for Hirschsprung disease
Celiac disease	At 2 years or with symptoms	Screen with IgA and tissue transglutaminase antibodies
Hematologic disease	At birth and in adolescence or if symptoms develop	Increased risk for neonatal polycythemia (18%), leukemoid reaction, leukemia (<1%)
Hypothyroidism	Birth; repeat at 6-12 mo and **annually**	Congenital (1%) and acquired (5%)
Growth and development	At each visit Use Down syndrome growth curves	Discuss school placement options Proper diet to avoid obesity
Obstructive sleep apnea	Start at ~1 yr and at each visit	Monitor for snoring, restless sleep
Atlantoaxial	At each visit by history and physical exam Radiographs at 3-5 years or when planning to	

subluxation or instability (incidence 10-30%)	participate in contact sports Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness) Many are asymptomatic	Special Olympics recommendations are to screen for high risk sports, e.g., diving, swimming, contact sports
Gynecologic care	Adolescent girls	Menstruation and contraception issues
Recurrent infections	When present	Check IgG subclass and IgA levels
Psychiatric, behavioral disorders	At each visit	Depression, anxiety, obsessive compulsive disorder, schizophrenia seem in 10-17% Autism spectrum disorder in 5-10% Early-onset Alzheimer disease

Extracted from Committee on Genetics: Health supervision for children with Down syndrome, Pediatrics 107:442–449, 2001; and Baum RA, Spader M, Nash PL, et al: Primary care of children and adolescents with Down syndrome: an update, Curr Prob Pediatr Adolesc Health Care 38:235–268, 2008.

IgA, immunoglobulin A; IgG, immunoglobulin G.

The majority of children with Down syndrome do not have behavior problems. It is estimated that psychiatric comorbidity is 18-38% in this population. These estimates are higher than in unaffected children, but they are lower than in children with similar levels of mental retardation from other etiologies. All maladaptive behaviors in persons with Down syndrome are thought to be inherently linked to cognitive impairment. Common behavioral difficulties that occur in children with Down syndrome include inattentiveness, stubbornness, and a need for routine and sameness. Aggression and self-injurious behavior are less common in this population. All of these behaviors can respond to educational or pharmacologic interventions.

The life expectancy for children with Down syndrome is reduced and is approximately 50 to 55 yr. Little prospective information about the secondary medical problems of adults with Down syndrome is known. Retrospective studies have shown premature aging and an increased risk of Alzheimer disease in adults with Down syndrome. These studies have also shown unexpected negative associations between Down syndrome and other medical comorbidities. Persons with Down syndrome have fewer than expected deaths caused by solid tumors and ischemic heart disease. This same study reported increased risk of adult deaths due to congenital heart disease, seizures, and leukemia. In 1 large study, leukemias accounted for 60% of all cancers in people with Down syndrome and 97% of all cancers in children with Down syndrome. There was decreased risk of solid tumors in all age groups, including neuroblastomas and nephroblastomas in children with Down syndrome and epithelial tumors in adults with Down syndrome.

Most adults with Down syndrome are able to perform activities of daily living. However, most adults with Down syndrome have difficulty with complex financial, legal, or medical decisions. In most circumstances, a conservator is appointed for the adult with Down syndrome.

This risk of having a child with trisomy 21 is highest in women who conceive at >35 yr of age. Even though younger women have a lower risk, they represent half of all mothers with babies with Down syndrome because of their higher overall birth rate. *All women should be offered screening for Down syndrome* in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin (β-hCG), unconjugated estriol, inhibin, and α-fetoprotein). This is known as the *quad screen;* it can detect up to 80% of Down syndrome pregnancies compared to 70% in the triple screen. Both tests have a 5% false-positive rate. There is a method of screening during the 1st trimester using fetal nuchal translucency (NT) thickness that can be done alone or in conjunction with maternal serum β-hCG and pregnancy-associated plasma protein-A (PAPP-A). In the 1st trimester, NT alone can detect ≤70% of Down syndrome

pregnancies, but with β-hCG and PAPP-A, the detection goes up to 87%. If both 1st and 2nd trimester screens are combined using NT and biochemical profiles (integrated screen), the detection rate goes up to 95%. If only 1st trimester quad screening is done, α-fetoprotein (MSAFP, which is decreased in affected pregnancies) is recommended as a 2nd trimester follow-up. Detection of fetal DNA in maternal plasma may also be diagnostic. The prenatal screens are also useful for other trisomies, although the detection rates are different from those given for Down syndrome.

In approximately 95% of the cases of Down syndrome there are 3 copies of chromosome 21. The origin of the supernumerary chromosome 21 is maternal in 97% of the cases as a result of errors in meiosis. The majority of these occur in maternal meiosis I (90%). Approximately 1% of persons with trisomy 21 are mosaics, with some cells having 46 chromosomes, and another 4% of have a **translocation** that involves chromosome 21. The majority of translocations in Down syndrome are fusions at the centromere between chromosomes 13, 14, 15, 21, and 22 known as *Robertsonian translocations.* The translocations can be de novo or inherited. Very rarely is Down syndrome diagnosed in a patient with only a part of the long arm of chromosome 21 in triplicate **(partial trisomy).** Isochromosomes and ring chromosomes are other rarer causes of trisomy 21. Down syndrome patients without a visible chromosome abnormality are the least common. It is not possible to distinguish the phenotypes of persons with full trisomy 21 and those with a translocation. Representative genes on chromosome 21 and their potential effects on development are noted in Table 76-8. Patients who are mosaic tend to have a milder phenotype.

Table 76-8 -- GENES LOCALIZED TO CHROMOSOME 21 THAT POSSIBLY AFFECT BRAIN DEVELOPMENT, NEURONAL LOSS, AND ALZHEIMER TYPE NEUROPATHOLOGY

SYMBOL	NAME	POSSIBLE EFFECT IN DOWN SYNDROME	FUNCTION
SIM2	Single-minded homolog 2	Brain development	Required for synchronized cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development	Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamideformyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development	Expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development	Function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease	Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic kainite1	Neuronal loss	Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer type neuropathy	Seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein β (neural)	Alzheimer type neuropathy	Stimulates glial formation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated aging?	Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and

			oxygen

Chromosome analysis is indicated in every person suspected of having Down syndrome. If a translocation is identified, parental chromosome studies must be performed to determine whether 1 of the parents is a translocation carrier, which carries a high recurrence risk for having another affected child. That parent might also have other family members at risk. Translocation (21;21) carriers have a 100% recurrence risk for a chromosomally abnormal child, and other Robertsonian translocations, such as t(14;21), have a 5-7% recurrence risk when transmitted by females. Genomic dosage imbalance contributes through direct and indirect pathways to the Down syndrome phenotype and its phenotypic variation.

Tables 76-9 and 76-10 provide more information on other aneuploidies and partial autosomal aneuploidies (Figs. 76-11 to 76-14).

Table 76-9 -- OTHER RARE ANEUPLOIDIES AND PARTIAL AUTOSOMAL ANEUPLOIDIES

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable The majority of patients are mosaics Deep palmar and plantar furrows are characteristic
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%)
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Known as Pallister-Killian syndrome. Sparse anterior scalp hair, eyebrows, and eyelashes, prominent forehead, chubby cheeks, long philtrum with thin upper lip and cupid-bow configuration, polydactyly, and streaks of hyper- and hypopigmentation

Table 76-10 -- FINDINGS THAT MAY BE PRESENT IN TRISOMY 13 AND TRISOMY 18

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60%-80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples
EXTREMITIES	

	Limited hip abduction
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth retardation Renal abnormalities Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth retardation Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

From Behrman RE, Kliegman RM: Nelson essentials of pediatrics, ed 4, Philadelphia, 2002, WB Saunders, p 142.

VSD, ventricular septal defect; PDA, patent ductus arteriosus; ASD, atrial septal defect.

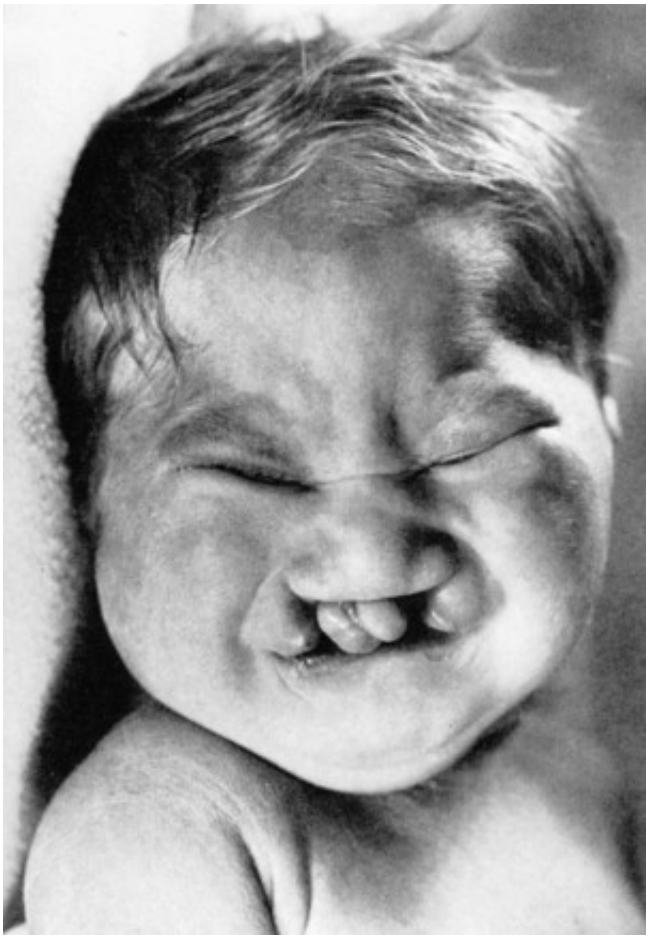

Figure 76-11 Facial appearance of a child with trisomy 13.
(From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St Louis, 1989, Mosby.)

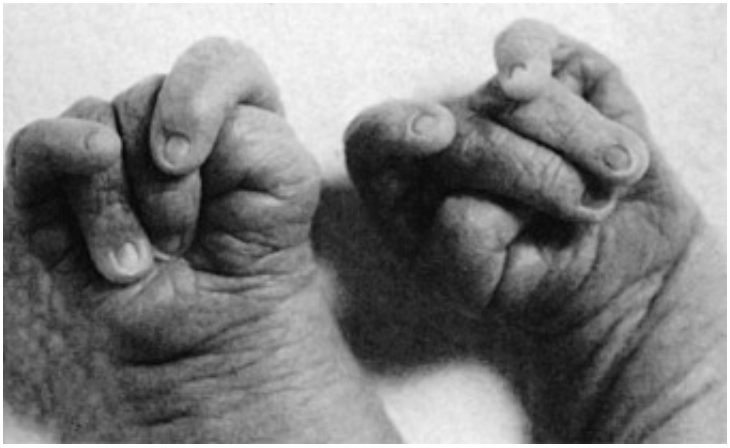

Figure 76-12 Trisomy 18: overlapping fingers and hypoplastic nails.
(From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St Louis, 1989, Mosby.)

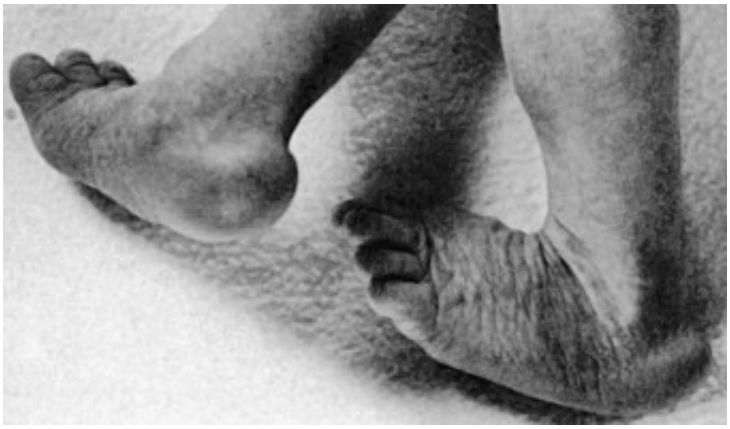

Figure 76-13 Trisomy 18: rocker-bottom feet (protruding calcanei).
(From Wiedemann HR, Kunze J, Dibbern H: Atlas of clinical syndromes: a visual guide to diagnosis, ed 3, St Louis, 1989, Mosby.)

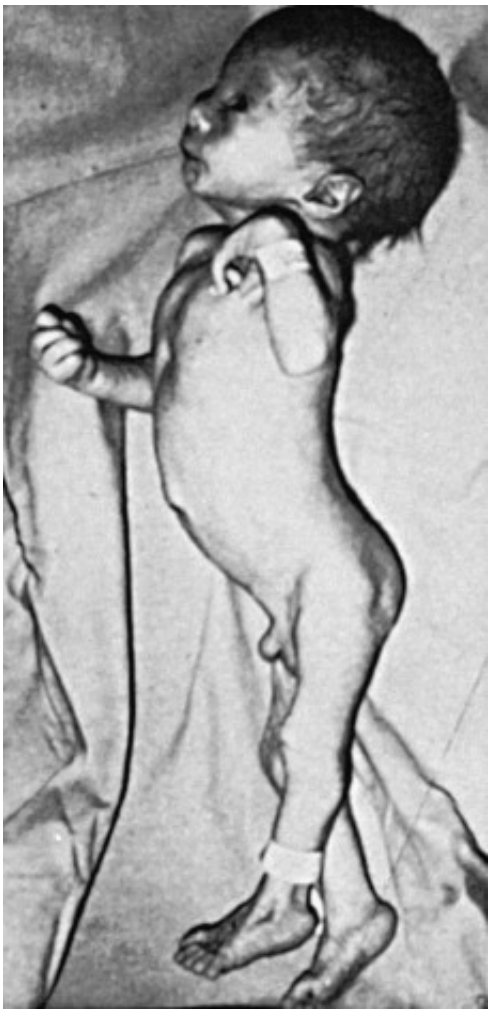

Figure 76-14 Male infant with trisomy 18 at age 4 days. Note prominent occiput, micrognathia, low-set ears, short sternum, narrow pelvis, prominent calcaneus, and flexion abnormalities of the fingers.