Genetics of Down Syndrome

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Introduction

Background

- In 1866, Down described clinical characteristics of the syndrome that now bears his name.
- In 1959, Lejeune and Jacobs et al independently determined that trisomy 21 is the cause.[1,2]
- Down syndrome is by far the most common and best known chromosomal disorder in humans and the most common cause of intellectual disability.[3]
- Mental retardation, dysmorphic facial features, and other distinctive phenotypic traits characterize the syndrome (see images below for examples).
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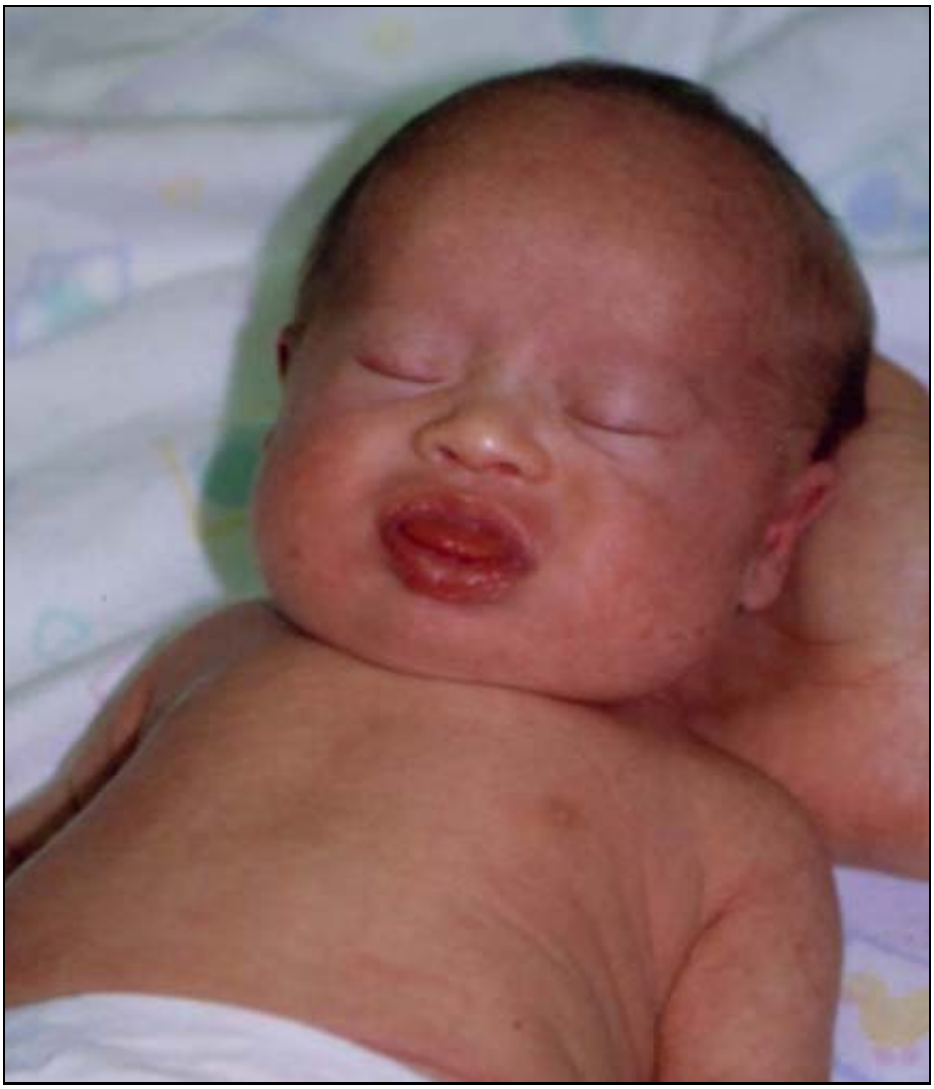

Infant with Down syndrome. Note up-slanting palpebral fissures, bilateral epicanthal folds, flat nasal bridge, open mouth with tendency of tongue protrusion, and small ear with overfolded helix.

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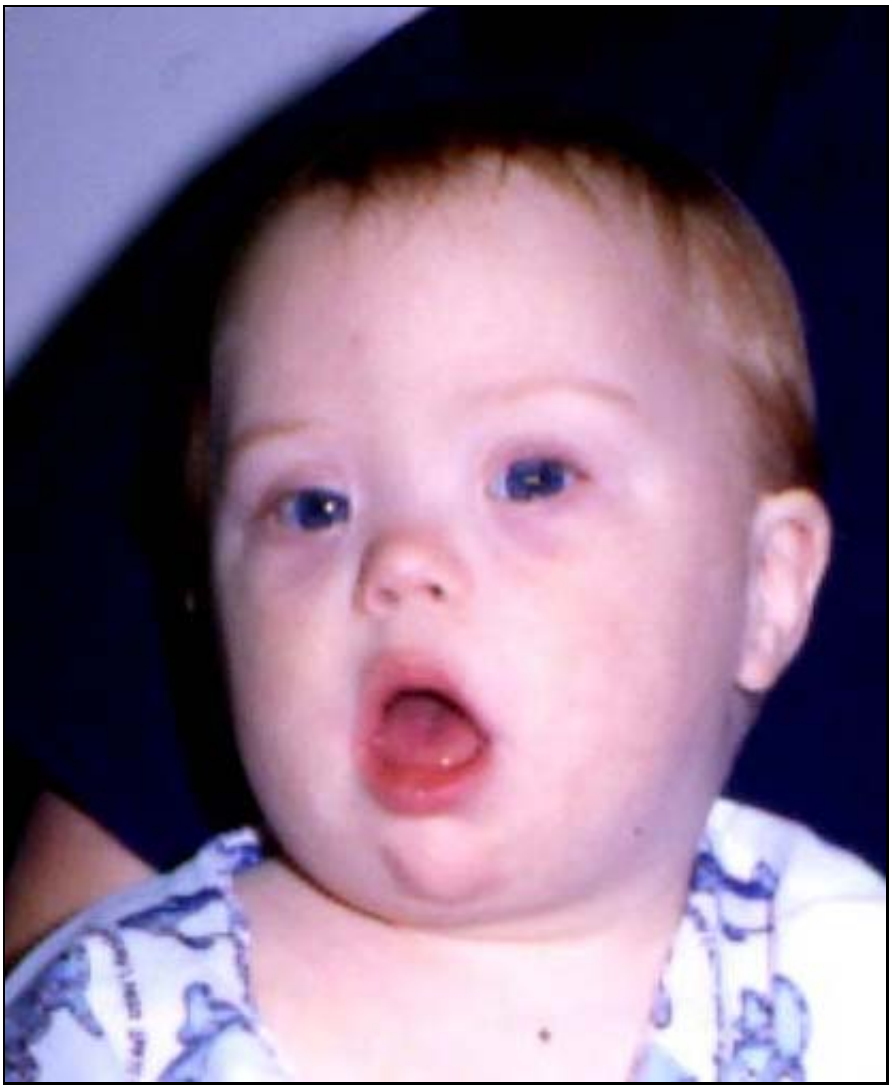


Child with Down syndrome. Note up-slanting palpebral fissures, bilateral epicanthal folds, a small nose with flat nasal bridge, open mouth with tendency for tongue protrusion, and small ears with overfolded helix.

Pathophysiology

- The extra chromosome 21 affects almost every organ system and results in a wide spectrum of phenotypic consequences. These include life-threatening complications, clinically significant alteration of life course (eg, mental retardation), and dysmorphic physical features. Down syndrome decreases prenatal viability and increases prenatal and postnatal morbidity. Affected children have delays in physical growth, maturation, bone development, and dental eruption.
- The extra copy of the proximal part of 21q22.3 appears to result in the typical physical phenotype: mental retardation, characteristic facial features, hand anomalies, and congenital heart defects. Molecular analysis reveals that the 21q22.1-q22.3 region, or Down syndrome critical region (DSCR), appears to contain the gene or genes responsible for the congenital heart disease observed in Down syndrome. A new gene, *DSCR1*, identified in region 21q22.1-q22.2, is highly expressed in the brain and the heart and is a candidate for involvement in the pathogenesis of Down syndrome, particularly, in the mental retardation and/or cardiac defects.

- Abnormal physiologic functioning affects thyroid metabolism and intestinal malabsorption. Frequent infections are presumably due to impaired immune responses, and the incidence of autoimmunity, including hypothyroidism and rare Hashimoto thyroiditis, is increased.
- Patients with Down syndrome have decreased buffering of physiologic reactions, resulting in hypersensitivity to pilocarpine and abnormal responses on sensory-evoked electroencephalographic tracings. Children with leukemic Down syndrome also have hyperreactivity to methotrexate. Decreased buffering of metabolic processes results in a predisposition to hyperuricemia and increased insulin resistance. Diabetes mellitus develops in many affected patients. Premature senescence causes cataracts and Alzheimer disease. Leukemoid reactions of infancy and an increased risk of acute leukemia indicate bone-marrow dysfunction.
- Children with Down syndrome are predisposed to developing leukemia, particularly transient myeloproliferative disorder and acute megakaryocytic leukemia. Nearly all children with Down syndrome who develop these types of leukemia have mutations in the hematopoietic transcription factor gene, *GATA1*. Leukemia in children with Down syndrome requires at least 3 cooperating events: trisomy 21, a *GATA1* mutation, and a third undefined genetic alteration.

Frequency

United States

- The frequency is about 1 case in 800 live births.
- Each year, approximately 6000 children are born with Down syndrome.[4]

Mortality/Morbidity

- Approximately 75% of concepti with trisomy 21 die in embryonic or fetal life. Approximately 85% of infants survive to age 1 year, and 50% can be expected to live longer than age 50 years. Congenital heart disease is the most important factor that determines survival. In addition, esophageal atresia with or without transesophageal (TE) fistula, Hirschsprung disease, duodenal atresia, and leukemia contribute to mortality. The high mortality rate later in life may be the result of premature aging.
- Individuals with Down syndrome have a greatly increased morbidity rate, primarily because of infections involving impaired immune response. Large tonsils and adenoids, lingual tonsils, choanal stenosis, or glossoptosis can obstruct the upper airway. Airway obstruction can cause serous otitis media, alveolar hypoventilation, arterial hypoxemia, cerebral hypoxia, and pulmonary arterial hypertension with resulting cor pulmonale and heart failure.
- A delay in recognizing atlantoaxial and atlanto-occipital instability may result in irreversible spinal-cord damage. Visual and hearing impairments in addition to mental retardation may further limit the child's overall function and may prevent him or her from participating in important learning processes and developing appropriate language and interpersonal skills. Unrecognized thyroid dysfunction may further compromise CNS function.

Race

- No racial predilection is known.

Sex

- The male-to-female ratio is increased (approximately 1.15:1) in newborns with Down syndrome. This effect is restricted to free trisomy 21.

Age

- Down syndrome can be diagnosed prenatally with amniocentesis, percutaneous umbilical blood sampling (PUBS), chorionic villus sampling (CVS), and extraction of fetal cells from the maternal circulation.
- Shortly after birth, Down syndrome is diagnosed by recognizing dysmorphic features and the distinctive phenotype.

Clinical

History

When recording the history from the parents of a child with Down syndrome, the clinician should include the following:[5]

- Parental concern about hearing, vision, developmental delay, respiratory infections, and other problems
- Feeding history to ensure adequate caloric intake
- Prenatal diagnosis of Down syndrome
- Vomiting secondary to GI tract blockage by duodenal web or atresia
- Absence of stools secondary to Hirschsprung disease
- Delay in cognitive abilities, motor development, language development (specifically expressive skills), and social competence
- Arrhythmia, fainting episodes, palpitations, or chest pain secondary to heart lesion
- Symptoms of sleep apnea, including snoring, restlessness during sleep, difficulty awaking, daytime somnolence, behavioral changes, and school problems

Symptoms of atlantoaxial instability include the following:

- About 13-14% of patients have radiographic evidence of atlantoaxial instability but no symptoms.
- Only 1-2% of patients have symptoms that require treatment.
- Symptoms include easy fatigability, neck pain, limited neck mobility or head tilt, torticollis, difficulty walking, change in gait pattern, loss of motor skills, incoordination, clumsiness, sensory deficits, spasticity, hyperreflexia, clonus, extensor-plantar reflex, loss of upper-body strength, abnormal neurologic reflexes, change in bowel and bladder function, increased muscle tone in the legs, and changes in sensation in the hands and feet.
- These symptoms often remain relatively stable for months or years.
- In rare cases, the symptoms progress to paraplegia, hemiplegia, quadriplegia, or death.

Physical

Growth

Short stature and obesity occurs during adolescence.

CNS

Moderate-to-severe mental retardation occurs, with an intelligence quotient (IQ) of 20-85 (mean, approximately 50). Hypotonia improves with age. Articulatory problems are present. Sleep apnea occurs when inspiratory airflow from the upper airway to the lungs is impeded for 10 seconds or longer; it often results in hypoxemia or hypercarbia.

Behavior

Natural spontaneity, genuine warmth, cheerful, gentleness, patience, and tolerance are characteristics. A few patients exhibit anxiety and stubbornness.

Seizure disorder (5-10%)

Infantile spasms are the most common seizures observed in infancy, whereas tonic-clonic seizures are most common in older patients.

Premature aging

Decreased skin tone, early graying or loss of hair, hypogonadism, cataracts, hearing loss, age-related increase in hypothyroidism, seizures, neoplasms, degenerative vascular disease, loss of adaptive abilities, and increased risk of senile dementia of Alzheimer type are observed.

Skull

Brachycephaly, microcephaly, a sloping forehead, a flat occiput, large fontanels with late closure, a patent metopic suture, absent frontal and sphenoid sinuses, and hypoplasia of the maxillary sinuses occur.

Eyes

Up-slanting palpebral fissures, bilateral epicanthal folds, Brushfield spots (speckled iris), refractive errors (50%), strabismus (44%), nystagmus (20%), blepharitis (33%), conjunctivitis, tearing from stenotic nasolacrimal ducts, congenital cataracts (3%), pseudopapilledema, spasm nutans, acquired lens opacity (30-60%), and keratoconus in adults are observed.

Nose

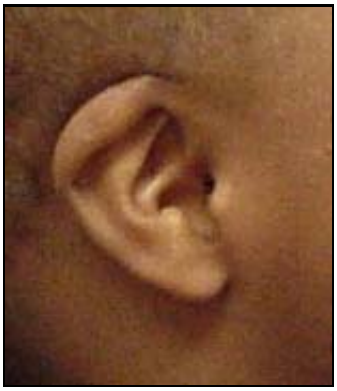
Hypoplastic nasal bone and flat nasal bridge are typical characteristics.

Mouth and teeth

An open mouth with a tendency of tongue protrusion, a fissured and furrowed tongue, mouth breathing with drooling, a chapped lower lip, angular cheilitis, partial anodontia (50%), tooth agenesis, malformed teeth, delayed tooth eruption, microdontia (35-50%) in both the primary and secondary dentition, hypoplastic and hypocalcified teeth, malocclusion, taurodontism (0.54-5.6%), and increased periodontal destruction are noted.

Ears

The ears are small with an overfolded helix (see the image below). Chronic otitis media and hearing loss are common. About 66-89% of children have a hearing loss of greater than 15-20 dB in at least 1 ear, as assessed by means of the auditory brainstem response (ABR).



Ear of an infant with Down syndrome. Note the characteristic small ear with overfolded helix.

Neck

Atlantoaxial instability (14%) can result from laxity of transverse ligaments that ordinarily hold the odontoid process close to the anterior arch of the atlas. Laxity can cause backward displacement of the odontoid process, leading to spinal cord compression in about 2% of children with Down syndrome.

Chest

The internipple distance is decreased.

Congenital heart defects

Congenital heart defects are common (40-50%); they are frequently observed in patients with Down syndrome who are hospitalized (62%) and are a common cause of death in this aneuploidy in the first 2 years of life.

The most common congenital heart defects are endocardial cushion defect (43%), ventricular septal defect (32%), secundum atrial septal defect (10%), tetralogy of Fallot (6%), and isolated patent ductus arteriosus (4%). About 30% of patients have several cardiac defects. The most common lesions are patent ductus arteriosus (16%) and pulmonic stenosis (9%). About 70% of all endocardial cushion defects are associated with Down syndrome.

Abdomen

Diastasis recti and umbilical hernia occur.

GI system (12%)

Duodenal atresia or stenosis, Hirschsprung disease (<1%), TE fistula, Meckel diverticulum, imperforate anus, and omphalocele are observed.

The prevalence rate of celiac disease in individuals with Down syndrome is reportedly 5-15% in different European and

US studies. Celiac disease occurs in genetically susceptible individuals, specifically those who have the human leukocyte antigen (HLA) heterodimers DQ2 (observed in 86-100% of individuals with celiac disease) and DQ8. These are strong linkages with high sensitivity and poor specificity.

Genitourinary tract

Renal malformations, hypospadias, micropenis, and cryptorchidism occur.

Skeleton

Short and broad hands, clinodactyly of the fifth fingers with a single flexion crease (20%), hyperextensible finger joints, increased space between the great toe and the second toe, and acquired hip dislocation (6%) are typical presentations.

Endocrine system

Hashimoto thyroiditis that causes hypothyroidism is by far the most common acquired thyroid disorder in patients with Down syndrome.[6] The onset is usually from school age onwards, but onset in infancy is reported.[7]

More rarely, Hashimoto thyroiditis can cause hyperthyroidism[8]; the incidence of Graves disease is also increased.[9]

The prevalence rate of thyroid disorders, such as congenital hypothyroidism, primary hypothyroidism, autoimmune thyroiditis, and compensated hypothyroidism or hyperthyrotropinemia, is reportedly 3-54% in individuals with Down syndrome and increases with increasing age.

Diabetes and decreased fertility can occur.

Hematologic system

Children with Down syndrome have an increased risk of developing leukemias, including acute lymphoblastic leukemia and myeloid leukemia;[10] However, the risk of cancer in general is not increased because of a reduced propensity for solid tumors.[11,12] Approximately 10% of newborns with Down syndrome develop a preleukemic clone, originating from myeloid progenitors in the fetal liver that is characterized by a somatic mutation in *GATA1*, which is localized on the X-chromosome. Mutations in this transcription factor lead to a truncated mutant protein GATA1short or GATA1s.[13,14] This preleukemia is referred to as transient leukemia (TL), transient myeloproliferative disease (TMD), or transient abnormal myelopoiesis (TAM)

The relative risk of acute leukemia in the first 5 years of life is 56 times that of individuals without Down syndrome. Approximately one in 150 patients develops leukemia. Neonatal leukemoid reactions (ie, pseudoleukemia) are common, and distinguishing this from true leukemia frequently poses a diagnostic challenge.

TMD is a hematologic abnormality that primarily affects infants with Down syndrome in the neonatal period.[15,16] TMD is characterized by an excessive proliferation of myeloblast cells in the infant's blood and bone marrow.[17] Approximately 10% of infants with Down syndrome have TMD.[18] However, this estimate probably identifies only patients with symptoms severe enough to warrant a CBC count and in whom the presence of blasts was of concern to the primary care provider.[19] An estimated 25% of infants with Down syndrome who present with TMD develop megakaryocytic leukemia 1-3 years later.[20] TMD is associated with pancytopenia, hepatosplenomegaly, and circulating immature WBCs. TMD spontaneously regresses within the first 3 months of life. However, in some children, it can be life threatening.[21,22] Despite the high rate of spontaneous regression, TMD can be a preleukemic disorder in 20-30% of children with Down syndrome.

Acute myeloid leukemia is as common in these individuals as acute lymphoid leukemia. Acute megakaryocytic leukemia is the most common form of acute myeloid leukemia in affected children and is uncommon in children who do not have Down syndrome.

Although the risk for leukemia is higher in individuals with Down syndrome, these patients have a lower risk of developing solid tumors, with the exception of germ cell tumors and, perhaps, retinoblastomas and lymphomas.

The patient's risk of carrying hepatitis B is increased if previously institutionalized.

Immunodeficiency

Patients have about a 12-fold increased risk of infectious diseases, especially pneumonia, because of impaired cellular immunity.

Skin

Xerosis, localized hyperkeratotic lesions, elastosis serpiginosa, alopecia areata (<10%), vitiligo, folliculitis, abscess formation, and recurrent skin infections are observed.

Dermatoglyphics

Distal axial triradius in the palms, transverse palmar creases, a single flexion crease in the fifth finger, ulnar loops (often 10), a pattern in hypothenar, and interdigital III regions are observed.

Neurobehavioral disorders

Most children with Down syndrome do not have a coexisting psychiatric or behavioral disorder. The available estimates of psychiatric comorbidity range from 18-38%. The disorders include attention deficit hyperactivity disorder, oppositional defiant disorder, nonspecific disruptive disorder, autism spectrum disorders, and stereotypical movement disorder in prepubertal children with Down syndrome and depressive illness, obsessive-compulsive disorder, and psychoticlike disorder in adolescents and adults with Down syndrome.

Trisomy 21 mosaicism

Trisomy 21 mosaicism can present with absent or minimal manifestations of Down syndrome and may be underdiagnosed as a cause of early-onset Alzheimer disease.[23]

The phenotype of persons having mosaicism for trisomy 21 and Down syndrome reflects the percentage of trisomic cells present in different tissues.[24]

Causes

The cause of Down syndrome is full trisomy 21 in 94% of patients. Mosaicism (2.4%) and translocations (3.3%) account for the rest. Approximately 75% of the unbalanced translocations are de novo, and approximately 25% result from familial translocation.

The most common error is maternal nondisjunction in the first meiotic division, with meiosis I errors occurring 3 times as frequently as meiosis II errors. The remaining cases are paternal in origin, and meiosis II errors predominate.

Most mosaic cases result from a trisomic zygote with mitotic loss of one chromosome, resulting in 2 different cell lines, one with 3 copies of chromosome 21 and one with 2 copies.

Translocation cases occur when genetic material from chromosome 21 becomes attached to another chromosome, resulting in 46 chromosomes with one chromosome having extra material from chromosome 21 attached.

Advanced maternal age remains the only well-documented risk factor for maternal meiotic nondisjunction. However, understanding of the basic mechanism behind the maternal age effect is lacking.

- With a maternal age of 35 years, the risk is 1 in 385.
- With a maternal age of 40 years, the risk is 1 in 106.
- With a maternal age of 45 years, the risk is 1 in 30.

Cytogenetic and molecular studies suggest that dup21(q22.1-22.2) is sufficient to cause Down syndrome. The DSCR contains genes that code for enzymes, such as superoxide dismutase 1 (SOD1), cystathionine beta-synthase (CBS), glycinamide ribonucleotide synthase-aminoimidazole ribonucleotide synthase-glycinamide formyl transferase (GARS-AIRS-GART).

Differential Diagnoses

Trisomy 18

Other Problems to Be Considered

49,XXXXY chromosome
Other high-order multiple X chromosomes
Zellweger syndrome
Other peroxisomal disorders

Workup

Laboratory Studies

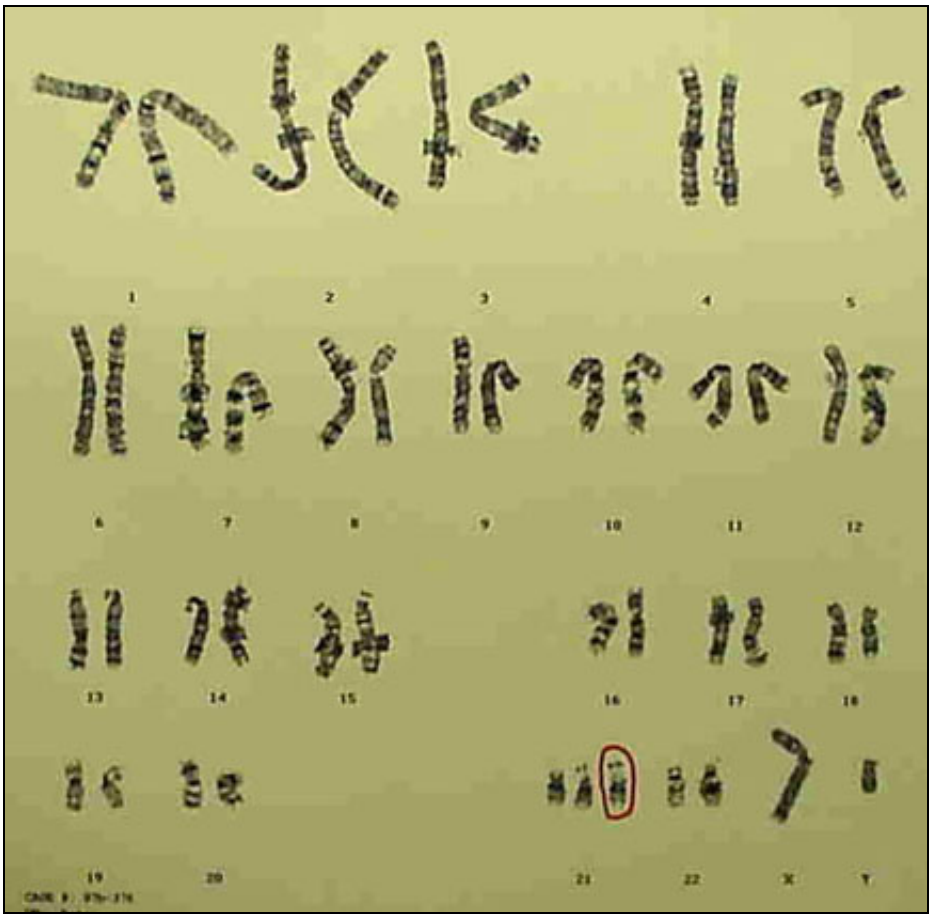
The following studies may be indicated in Down syndrome:

Cytogenetic studies

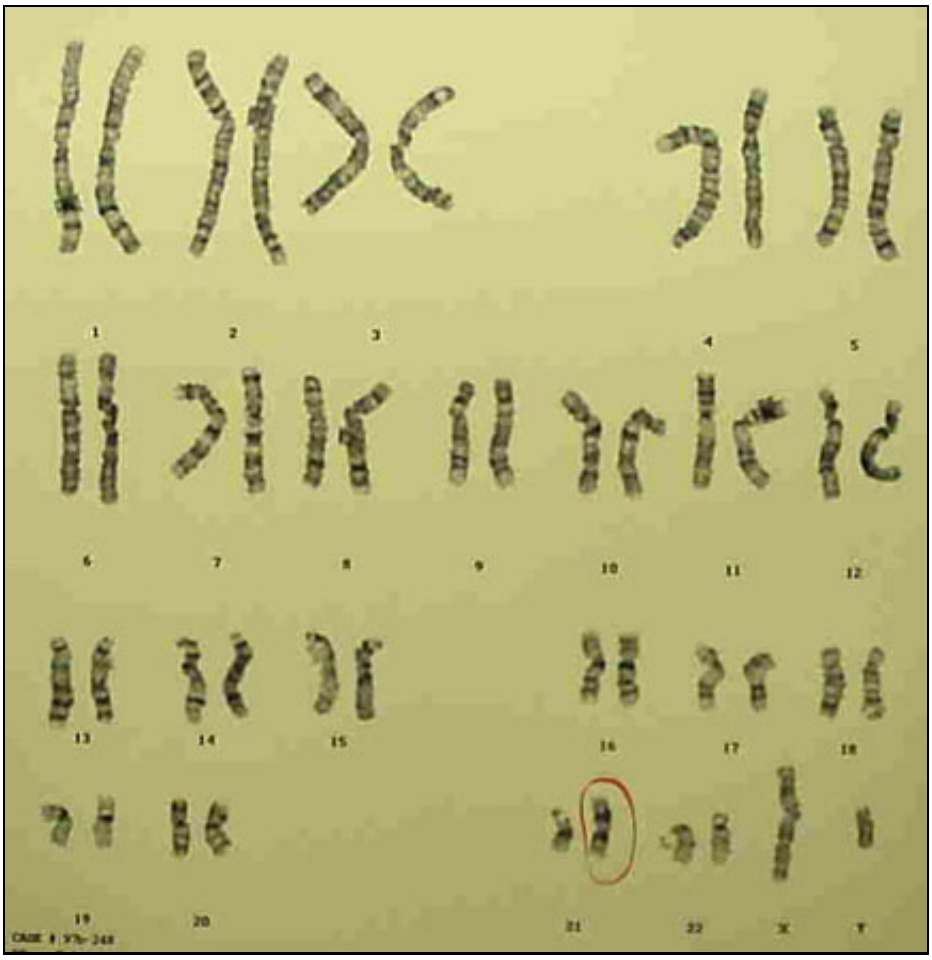
The clinical diagnosis should be confirmed with cytogenetic studies.

Karyotyping is essential to determine the risk of recurrence.

In translocation Down syndrome, karyotyping of the parents and other relatives is required for proper genetic counseling (see the images below).



G-banded karyotype showing trisomy 21 (47,XY,+21).



G-banded karyotype showing trisomy 21 of isochromosome arm 21q type [46,XY,i(21)(q10)].

Interphase fluorescence in situ hybridization (FISH)

FISH may be used for rapid diagnosis. It can be successful in both prenatal diagnosis and diagnosis in the neonatal period.

Occult mosaicism for trisomy 21 may partially explain the previously described association between family history of Down syndrome and risk of Alzheimer disease. Screening for mosaicism with FISH is indicated in selected patients with mild developmental delay and those with early onset Alzheimer disease.[23]

Evaluation of the proportion of cells with trisomy 21 in mosaic trisomy 21[24]

- Lymphocyte preparations
- Buccal mucosa cellular preparations
- FISH methodology
- Scoring frequency of trisomic cells

Thyroid function tests

Thyroid-stimulating hormone (TSH) and thyroxine (T4) levels should be obtained at birth and annually thereafter.

Measurement of immunoglobulin G (IgG)

This test is used to identify a deficiency of subclasses 2 and 4. Decreased levels of IgG subclass 4 is significantly correlated with bacterial infections. These deficits in cellular immunity have also been documented in individuals with gingivitis and periodontal disease.

Hematologic tests

These include CBC count with differential and bone marrow examination.

Papanicolaou test (Pap smear)

Perform Pap smears every 1-3 years in sexually active women starting at the age of first intercourse.

Imaging Studies

Skeletal radiography

Craniofacial anomalies include brachycephalic microcephaly and hypoplastic facial bones and sinuses.

Cervical radiography (with lateral flexion and extension views) is required to measure the atlantodens distance and to rule out atlantoaxial instability at the age of 3 years. Radiography is also used before anesthesia is given if signs suggest spinal cord compression.

Reduced iliac and acetabular angles may be present in young infants.

Short hands with shortened digits and clinodactyly due to hypoplastic middle phalanx of the fifth finger may be present.

Echocardiography

This test should be performed on all infants with Down syndrome to identify congenital heart disease, regardless of findings on physical examination.

Mammography

Obtain yearly mammograms in women older than 50 years.

Other Tests

Auditory brainstem response (ABR) testing

Also known as brainstem auditory evoked response (BAER), the ABR demonstrates hearing loss. Evaluation of the ABR in 47 nonselected children with Down syndrome aged 2 months to 3.5 years indicated some hearing loss in 66% (28% unilateral, 38% bilateral).

Speech evaluation

This may also be indicated.

Ophthalmic examination

Pediatric ophthalmic examination should be performed for vision screening and for detecting ophthalmologic disorders.

Developmental chart

A developmental chart for noninstitutionalized children based on a modified Denver Developmental Screening Test is available for assessing developmental milestones.[25]

Growth charts

Growth charts are available for children with Down syndrome.

An increased incidence of celiac disease has been reported in Down syndrome.

Evaluation should be prompted by recognition of signs and symptoms, such as growth failure, abdominal pain, and loose stools.

Dental care

Rigorous dental hygiene and dental evaluation are indicated beginning after tooth eruption.

Treatment

Medical Care

Despite continued work, no notable medical treatments for mental retardation associated with Down syndrome have been forthcoming. However, the dramatic improvements in medical care described below have greatly improved the quality of life for patient and increased their life expectancy.

Genetic counseling

Trisomy 21

Previous history of trisomy can increase a woman's risk for a recurrence.[26]If the couple has a child with trisomy 21, the risk of recurrence is about 1%.[27]The risk does not appear to be increased in siblings of affected individuals.

Translocation Down syndrome

If the child has a translocation, a balanced translocation must be excluded in the parents.

Robertsonian translocation

The recurrence risk depends on the type of translocation. In most cases, the recurrence risk for de novo translocations is similar to that of the general population but may be slightly higher in some situations; it is estimated to be 2-3%.[28]

If either parent has a translocation, start additional family studies and counseling.

A parent with a balanced Robertsonian translocation is phenotypically normal but has an increased risk of having a chromosomally unbalanced offspring.

The theoretic recurrence risk for a Robertsonian carrier parent to have a liveborn offspring with Down syndrome is 1 in 3. However, only 10-15% of the progeny of carrier mothers and only 2-3% of the progeny of carrier fathers have Down syndrome. The reason for this difference is not clear.

In a carrier parent with a 21q21q translocation or isochromosome, the recurrence risk is 100%.

Mosaic Down syndrome

Most patients with mosaic Down syndrome were once trisomy 21 zygotes.

The phenotype varies and possibly reflects the variable proportion of trisomy 21 cells in the embryo during early development.

In rare instances, low-level mosaicism in germinal tissue of a parent is postulated to be the cause of more than one trisomic child in the family.

Reproduction

Affected individuals rarely reproduce.

About 15-30% of females with trisomy 21 are fertile and have a 50% risk of having an affected child. The literature contains reports of 4 pregnancies fathered by 3 male patients with Down syndrome.

Infertility in males has been attributed to defective spermatogenesis, but ignorance of the sexual act may be one of the contributing factors.

Vaccination and medication

Usual immunizations and well childcare should be performed as the American Academy of Pediatrics recommends.

Thyroid hormone for hypothyroidism is needed to prevent intellectual deterioration and improve the individual's overall function, academic achievement, and vocational abilities.

Subacute bacterial endocarditis prophylaxis is needed in susceptible children with cardiac disease when they undergo dental work or other invasive procedures.

Digitalis and diuretics are usually required for cardiac management.

Prompt treatment of respiratory tract infections and otitis media is necessary.

Children with chronic cardiac and respiratory disease are candidates for pneumococcal and influenza vaccination.

Administer anticonvulsants for tonic-clonic seizures or for infantile spasms (treat with steroids).

Provide pharmacologic agents, psychotherapy, and/or behavior therapies for psychiatric disorders.

Treat skin disorders with weight reduction, proper hygiene, frequent baths, application of antibiotic ointment, or systemic antibiotic therapy.

Prevent dental caries and periodontal disease through appropriate dental hygiene, fluoride treatments, good dietary habits, and restorative care.

Early intervention programs are promising. Programs for infants aged 0-3 years are designed to comprehensively monitor and enrich their development by focusing on feeding, as well as gross and fine motor, language, personal, and social development. Early intervention techniques may improve the patient's social quotient. Overall, positive developmental changes are observed in children with Down syndrome, particularly in terms of their independence, community functioning, and quality of life.

Megadoses of vitamins and minerals supplemented with zinc and/or selenium were not beneficial in a number of well-controlled scientific studies.

Children with Down syndrome and leukemia are more sensitive to some chemotherapeutic agents (eg, methotrexate) than other children. Thus, they require careful monitoring for toxicity.

Medical care and monitoring for the adolescent with Down syndrome

Perform annual audiologic evaluation.

Perform annual ophthalmologic evaluations for keratoconus or corneal opacities and/or cataracts.

Treat dermatologic issues, such as folliculitis, xerosis, atopic dermatitis, seborrheic dermatitis, fungal infections of skin and nails, vitiligo, and alopecia.

Prevent obesity by decreasing the patient's caloric intake and increasing activity (social and leisure).

Screen for celiac disease (symptoms such as constipation, diarrhea, bloating, poor growth, or weight loss) and treat the patient with a gluten-free diet.

Swallowing difficulties may persist through the adolescent years and must be addressed.

Antibiotic prophylaxis during dental and surgical procedures in the presence of mitral valve prolapse

Treatment options should include bone marrow transplantation if leukemia occurs.

Treat airway obstruction medically and surgically.

Special attention to perioperative modalities because of atlantoaxial instability and problems with the respiratory system.

Screen for hypothyroidism and diabetes mellitus.

Address concerns regarding menstrual hygiene, sexual abuse, pregnancy, and premenstrual syndrome.

Manage neurologic problems, including mental retardation, hypotonia, seizures, and strokes.

Continue speech and language therapy, with a focus on expressive language and intelligibility.

Evaluate and treat behavioral problems, such as disruptive behavior disorders, stereotypic behaviors, phobias,

elimination difficulties, autism, eating problems, self-injurious behavior, and Tourette syndrome.

Evaluate and treat psychiatric disorders, such as depression, and self-talk.

Assist the patient's eventual medical transition and occupational issues.

During adolescence, an additional 2% of patients die from complications of congenital heart disease, infections, leukemia, and accidents. Continue subacute bacterial endocarditis prophylaxis in adolescents with cardiac defects.

Repeat cervical spine radiography as needed for Special Olympics participation.

Discuss issues related to transition to adulthood.

Emphasize the importance of a well-balanced diet and routine exercise.

Review plans for school placement and plans after high-school graduation and future vocational plans.

Discuss plans for alternative long-term living arrangements such as community living arrangements. Parents should update estate planning and custody arrangements.

Encourage social and recreational programs with friends.

Discuss sexuality and socialization and the need for and degree of supervision required. Review options for contraception if the teen is sexually active. Make recommendations for routine gynecologic care.

Monitor the family's need for supportive care or counseling, respite care, and behavior management techniques. Facilitate referrals for respite care and treatment of parental problems.

Facilitate transfer to adult health care.

Surgical Care

Down syndrome alone does not adversely affect surgical outcomes in the absence of pulmonary hypertension.

Timely surgery of cardiac anomalies, which are common during the first 6 months of life, may be necessary to prevent serious complications.

Prompt surgical repair is necessary for GI anomalies, such as tracheoesophageal (TE) fistula, pyloric stenosis, duodenal atresia, annular pancreas, aganglionic megacolon, and imperforate anus.

Adenotonsillectomy may be performed to manage obstructive sleep apnea.

Surgical intervention may be necessary to reduce atlantoaxial subluxation and to stabilize the upper segment of the cervical spine if neurologic deficits are clinically significant.

Anesthetic airway management may be needed. Preoperative evaluation for anesthesia must include adequate evaluation of the airway and the patient's neurologic status. Cervical radiography (with flexion and extension views) should be performed when any neurologic deficit suggests spinal-cord compression. During laryngoscopy and intubation, the patient's head should be maintained in a neutral position, and hyperextension should be avoided. Anticholinergics can be prescribed to control hypersecretion in the airways. Other airway complications include subglottic stenosis and obstructive apnea, which may result from a relatively large tongue, enlarged adenoids, and midfacial hypoplasia.

Congenital cataracts occur in about 3% of children and must be extracted soon after birth to allow light to reach the retina. Afterward, appropriate correction with glasses or contact lenses helps ensure adequate vision.

Consultations

- Clinical geneticist
- Developmental pediatrician
- Cardiologist
- Ophthalmologist
- Neurosurgeon
- Orthopedic specialist
- Psychiatrist
- Physical and occupational therapist
- Speech-language pathologist
- Audiologist

Diet

- No special diet is required, unless celiac disease is present. A balanced diet and regular exercise are needed to maintain appropriate weight.
- Feeding problems and failure to thrive usually improve after cardiac surgery.

Activity

- No restriction of activities is necessary. Advise the patient to exercise to maintain an appropriate weight.
- Patients with symptoms of arrhythmia, episodes of fainting, abnormal findings on ECG, and palpitations or chest pain should refrain from participating in sports and strenuous exercise.
- Children with C1-C2 subluxation should be allowed to compete in the Special Olympics unless they have symptoms of cervical-cord compression.

Medication

- Drug therapy is not currently a component of the standard of care for Down syndrome.

Follow-up

Further Inpatient Care

- Manage cardiac defects medically or surgically in patients with Down syndrome.
- Regular screening is necessary for institutionalized older adults to diagnose early-onset dementia, epilepsy,

hypothyroidism, and early loss of visual acuity and hearing.

- Cytogenetic studies are necessary to confirm the clinical diagnosis.

Further Outpatient Care

- Audiologic evaluation for hearing loss
- Apnea monitoring

Inpatient & Outpatient Medications

- Diuretics and digoxin should be used to manage congestive heart failure secondary to congenital heart defect.

Complications

Medical complications include the following:[29]

Cardiac and cardiovascular[30]

Children who seem asymptomatic at birth and do not have a murmur may have a significant cardiac defect.

If increased pulmonary vascular resistance is noted, the left-to-right shunt may be minimized, thus preventing early heart failure. However, if left undetected, this condition may lead to persistent pulmonary hypertension with irreversible pulmonary vascular changes.

Generally, surgery to correct the heart defect is delayed until the infant is larger and is strong enough to tolerate the surgery, which is usually performed at age 6-9 months. Most children do very well and thrive following their surgery.

In patients with an atrioventricular septal defect, symptoms usually occur in infancy as a result of systemic-to-pulmonary shunting, high pulmonary blood flow, and an increased risk of pulmonary arterial hypertension. Increased pulmonary resistance may lead to a reversal of the systemic-to-pulmonary shunt accompanied by cyanosis (ie, Eisenmenger syndrome).

Patients with Down syndrome are considered to be at higher risk for pulmonary arterial hypertension compared with patients without Down syndrome. This is due to a diminished number of alveoli, a thinner media of pulmonary arterioles and an impaired endothelial function in these patients.

Early corrective cardiac surgery is warranted to prevent irreversible pulmonary vascular lung damage. Moreover, new medical treatment strategies (eg, prostacyclin, endothelin receptor antagonist and phosphodiesterase-5-inhibitor) have been demonstrated to substantially improve clinical status and life expectancy of patients with pulmonary arterial hypertension.

Coronary artery disease–related mortality is surprisingly low. Pathological studies revealed decreased levels of atherosclerosis in Down syndrome.

GI

Gastroesophageal reflux is commonly seen in children with Down syndrome and can be severe enough to result in aspiration of stomach contents, resulting in respiratory symptoms such as persistent coughing, wheezing, and pneumonia.

Infants with oral-motor difficulties may present with choking and gagging on feedings as well as the respiratory symptoms mentioned.

Celiac disease is more common in patients with Down syndrome than in those without.

Chronic constipation is common.

Obesity is common. Patients need to have specific dietary guidelines on caloric needs and portion sizes. An active lifestyle with routine exercises is recommended for the whole family. Children should be encouraged to participate in recreational activities such as swimming, dancing, walking, and playing outdoors.

Ophthalmologic

Common eye disorders include fractive errors, such as myopia, hyperopia, and astigmatism, which can be corrected with glasses if the child is willing to wear them. Other common eye disorders include strabismus and nystagmus.

Congenital cataracts can lead to blindness if left untreated.

Other serious eye disorders include glaucoma and keratoconus.

Blocked tear ducts, or nasolacrimal duct stenosis, is common and can lead to increased tear stasis and conjunctivitis.

Otolaryngologic

Many children experience recurrent ear infections or persistent middle ear effusions believed to be due to midfacial hypoplasia.

Early and aggressive treatment of chronic ear disease can greatly reduce hearing loss in children with Down syndrome.

Sinusitis and nasopharyngitis secondary to narrow nasal passages and sinuses.

Obstructive sleep apnea secondary to enlarged tonsils as well as other causes for upper airway obstruction.

Endocrine

Thyroid dysfunction, particularly hypothyroidism, is relatively common in Down syndrome.

Hyperthyroidism can also occur.

Diabetes mellitus occurs with higher frequency.

Hematologic

The spectrum of malignancies in patients with Down syndrome offers both insights and enigmas.[31] Patients with Down syndrome exhibit a unique pattern of malignancies, yielding intriguing insights into cancer biology. These patients also pose distinctive challenges to the oncologist because of their particular profile of treatment-related toxicities. Individuals with Down syndrome have a higher risk for leukemia, experiencing 3 distinct disease entities (ie, transient myeloproliferative disorder [TMD], acute megakaryoblastic leukemia [AML], and acute lymphoblastic leukemia [ALL]) and have a lower risk for solid tumors.

Childhood leukemia is relatively common: acute myelogenous leukemia is more common in infants, whereas acute lymphoblastic leukemia is more common in children older than 1 year.

Newborn infants with Down syndrome are prone to TMD, also known as leukemoid reaction, transient abnormal myelopoiesis, or transient leukemia; in some cases, it can progress to more severe disease, such as acute megakaryoblastic leukemia, within the first 4 years of life.

Immunologic

Children are more prone to recurrent respiratory and systemic infections secondary to deficiencies in some immunoglobulin levels.

Immunoglobulin (Ig)A deficiency as well as IgG subclasses can be seen in individuals with Down syndrome.

Individuals with Down syndrome are also more susceptible to autoimmune diseases such as thyroid disease, diabetes, and celiac disease.

Down syndrome has been associated with various autoimmune conditions. The thyroid gland is most commonly affected. Down syndrome is more frequently associated with hypothyroidism than hyperthyroidism.

Orthopedic

Approximately 20% of all patients with Down syndrome experience orthopedic problems.[32] Upper cervical spine instability has the most potential for morbidity and, consequently, requires close monitoring. Other conditions such as scoliosis, hip instability, patellar instability, and foot problems can cause disability if left untreated. In some of these conditions, early diagnosis can prevent severe disability.

Atlantoaxial instability, defined as increased mobility of the cervical spine at the level of the first and second vertebrae, can lead to subluxation of the cervical spine. Approximately 10-30% of individuals with Down syndrome have this condition.[33] Most are asymptomatic; however, 10% of individuals who have the condition have symptoms, including neck pain, torticollis, changes in gait, changes in bowel or bladder control, or other signs of paralysis or weakness.[34]

Joint dislocations due to ligamentous laxity and hypotonia are observed.

Other orthopedic conditions include genu valgus, over-pronation of the ankle, and flat feet.

Psychiatric and behavioral disorders

Psychiatric disorders are reported in 13-17.6% of children with Down syndrome;[35] these conditions include common psychiatric disorders such as depression, anxiety, obsessive-compulsive disorder, schizophrenia, and anorexia nervosa.

Other disruptive behavior disorders, such as attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, can also be present. Autism spectrum disorders deserve mention because they occur at higher rates in children with Down syndrome compared with the general population. Current evidence supports that autism affects 1 of every 150 children.[36]

Alzheimer disease or Alzheimer-type dementia can occur at a relative early age. The disease is characterized by memory loss, the inability to learn new information, and a decline in intellectual skills. Behavioral changes in Down syndrome diagnosed with Alzheimer dementia include the following:[37]

- Apathy
- Episodic noisy excitement
- Irritability
- Wandering and confusion
- Destructive, aggressive or difficult behavior
- Lethargy, withdrawal, loss of interest
- Silliness
- Limited response to people
- Social inadequacy, isolation
- Extreme changes in appetite (typically wight loss)
- Restlessness
- Sleep disturbance
- Incontinence
- Excessively uncooperative
- Anxiety and fearfulness
- Sadness
- Stealing and general regressive behavior
- Personality changes
- Increased dependence

Surgical complications include the following:[32]

- Surgical intervention in children with Down syndrome has a high risk of complications, particularly infection and wound healing problems.
- Careful anesthetic airway management is needed because of the associated risk of cervical spine instability.

Prognosis

- The overall outlook for individuals with Down syndrome has dramatically improved. Many adult patients are healthier, are better integrated into society, and have increased longevity than before. However, their life expectancy is still reduced.
- Congenital heart disease is the major cause for early mortality.
- Leukemia, thyroid diseases, autoimmune disorders, and susceptibility to infections related to an abnormal serum IgG subclass pattern are common.

- Many patients develop progressive Alzheimer-like dementia by age 40 years, and 75% of patients have signs and symptoms of Alzheimer disease.
- Relative preservation of cognitive and functional ability is associated with better survival in elderly persons with Down syndrome.[38] Clinically, the most important disorders in elderly persons with Down syndrome that are related to mortality are dementia, mobility restrictions, visual impairment, and epilepsy but not cardiovascular diseases. Also, the level of intellectual disability and institutionalization are associated with mortality.

Patient Education

Career preparation should include acquisition of job skills, choice of job area, development of work-support behavior, and opportunities for job mobility. The goal of successful transition from school to the world of work is meaningful employment and optimal function in the least restrictive environment.

Opportunities to participate in community life should be made available.

Individuals should be encouraged to pursue daily living tasks with minimal or no assistance.

Patients should participate in cultural, leisure, and recreational activities during the growing years.

Patients may qualify for supplemental security income (SSI) depending on their family's income.

A parent's guide to the genetics of Down syndrome is available.[39]

Additional resources can be obtained from the following organizations:

- The National Down Syndrome Society
  666 Broadway, 8th Floor
  New York, NY 10012-2317
  Phone: 212-460-9330 or 800-221-4602
  Fax: 212-979-2873
  E-mail: info@ndss.org
- National Down Syndrome Congress
  1370 Center Drive, Suite 102
  Atlanta, GA 30338
  Phone: 770-604-9500 or 800-232-NDSC
  E-mail: info@ndscenter.org
- National Association for Down Syndrome
  PO Box 206
  Wilmette, IL 60091
  Phone: 630-325-9112
- International Resource Center for Down Syndrome, Cleveland, OH
- The Arc
  The Arc of the United States
  1010 Wayne Avenue, Suite 650
  Silver Spring, MD 20910
  Phone: (301) 565-3842

- The Down Syndrome WWW page

For excellent patient education resources, visit eMedicine's Brain and Nervous System Center. Also, see eMedicine's patient education article Down Syndrome.

Miscellaneous

Medicolegal Pitfalls

- Failure to identify characteristic symptoms and signs of Down syndrome and to refer patient to a geneticist for evaluation and genetic counseling
- Failure to order chromosomal analysis when Down syndrome is clinically diagnosed
- Failure to offer prenatal screening to pregnant women
- Failure to offer prenatal diagnosis after a woman has an affected child
- Reliance on maternal serum triple-marker screening for prenatal diagnosis in a pregnancy at risk for Down syndrome (Amniocentesis and chronic villus sampling [CVS] are the criterion standard diagnostic tests for prenatal diagnosis in a pregnancy at increased risk.)

Special Concerns

Awareness

Physicians and parents should be aware of the range of psychomotor potential so that early intervention, schooling, and community placement are provided.

Prenatal screening

Advanced maternal age

The first prenatal diagnosis of Down syndrome was made in 1968, and screening women on the basis of advanced maternal age with amniocentesis was gradually introduced into medical practice.

Maternal serum biochemical markers

Low maternal serum alpha-fetoprotein (MSAFP) levels were associated with Down syndrome in 1983. Later, elevated human chorionic gonadotropin (hCG) and low unconjugated estriol (uE3) levels were found to be markers for Down syndrome. By 1988, use of the 3 biochemical markers, together with maternal age, had been accepted as a method of prenatal screening for Down syndrome in the general population. Currently, in the general population, maternal age, ultrasound findings, and maternal serum markers (first or second trimester) are used alone or in combination for risk calculation.[40]

When ultrasonography is used to estimate gestational age, the detection rate is about 20% when only the MSAFP test is used, 59% when the double test (MSAFP and hCG) is used, and 69% when the triple test (MSAFP, hCG, uE3) is used. The false-positive rate is 5%. Other factors for adjustment are maternal age and weight, insulin-dependent diabetes mellitus, multiple pregnancies, racial background, previous pregnancy with Down syndrome, and first or repeat test in a pregnancy. A positive screening result only suggests an increased risk for Down syndrome, and definitive testing with amniocentesis with chromosomal analysis is indicated.

In a retrospective study of first-trimester screening for free beta-hCG and pregnancy-associated plasma protein A (PAPP-A), detection rates were as high as those associated with MSAFP, hCG, or uE3 testing in the second trimester. Prospective studies are needed to further assess first-trimester screening.

Second-trimester maternal serum marker screening allows the detection of 60–70% of Down syndrome cases, with a false positive rate of 5%.[41]

Effective screening for trisomy 21 is provided by assessment of a combination of maternal age, fetal nuchal translucency thickness, and maternal serum free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 10-14 weeks' gestation.[42,43,44]Prospective studies have demonstrated that combined screening can identify about 90% of affected fetuses, with a false-positive rate of 5%.[45,46]

Among high-risk pregnancies clinically indicated for invasive prenatal diagnosis, noninvasive detection of fetal trisomy 21 can be achieved using multiplexed, massively parallel sequencing of maternal plasma DNA, with 100% sensitivity and 97.9% specificity; this provides a 96.6% positive predictive value and 100% negative predictive value.[47]The sequencing test could be used to rule out trisomy 21 in high-risk pregnancies before proceeding to invasive diagnostic testing to reduce the number of cases that require amniocentesis or chorionic villus sampling. However, its diagnostic performance and practical feasibility in the clinical setting has not been tested on a large scale.

In the nonstandard Down syndrome (mosaicism and translocation) cases, second-trimester maternal serum marker screening gave the same detection rate as for standard trisomy 21, except the cases with low-level mosaicism (<10%).[40]

Prenatal ultrasonography may reveal the following:

- Ultrasonography soft markers observed in the second trimester for Down syndrome include absent or hypoplastic nasal bone, thickened nuchal fold, echogenic bowel, shortened long bones, and pyelectasis.
- Absent or hypoplastic nasal bone is observed in 43-62% of trisomy 21 fetuses compared with 0.5-1.2% observed in normal fetuses.
- A thickened nuchal fold has been associated with a greatly increased risk of trisomy 21 and may be an early feature of fetal hydrops or cystic hygroma.
- Echogenic bowel has been observed in approximately 15% of fetuses with trisomy 21 compared with 0.6% observed in normal fetuses. About 35% of fetuses with true echogenic bowel have some underlying pathology, such as first trimester bleeding, fetal infections, and cystic fibrosis due to meconium ileus.
- Shortened long bones (humerus and femur) have been associated with an increased risk of chromosomal abnormalities. The humerus is a more reliable discriminator for Down syndrome than the femur. The humerus appears to be the next most important marker after nasal bone and nuchal fold. The other possible causes include skeletal dysplasia, especially if the long bones are severely shortened or abnormal in appearance (eg, bowing fractures or reduced mineralization).
- Pyelectasis has been observed in approximately 17% of fetuses with trisomy 21. Approximately 1 in every 300 fetuses with isolated pyelectasis has aneuploidy. Pyelectasis has been associated with an increased risk of hydronephrosis and postnatal urinary reflux.
- Other ultrasonography abnormalities include cystic hygroma, duodenal atresia or stenosis (double-bubble sign),

cardiac defects (endocardial cushion defect with atrial and ventricular septal defects and abnormal mitral and tricuspid valves), and intracardiac echogenic focus.

- Ultrasonography should not be relied on as the primary method of diagnosing Down syndrome, and the diagnosis can be missed in affected families.

Extraction of fetal cells from the maternal circulation: After fetal nucleated RBCs are sorted by using different cell transferrin and glycophorin-A receptors on the cell surface, interphase fluorescence in situ hybridization (FISH) can be used to determine the chromosomal constitution. Chromosome-specific probes available for X, Y, 13, 18, and 21 permit diagnosis. The FISH finding should be confirmed by using standard cytogenetic techniques.

Prenatal diagnosis

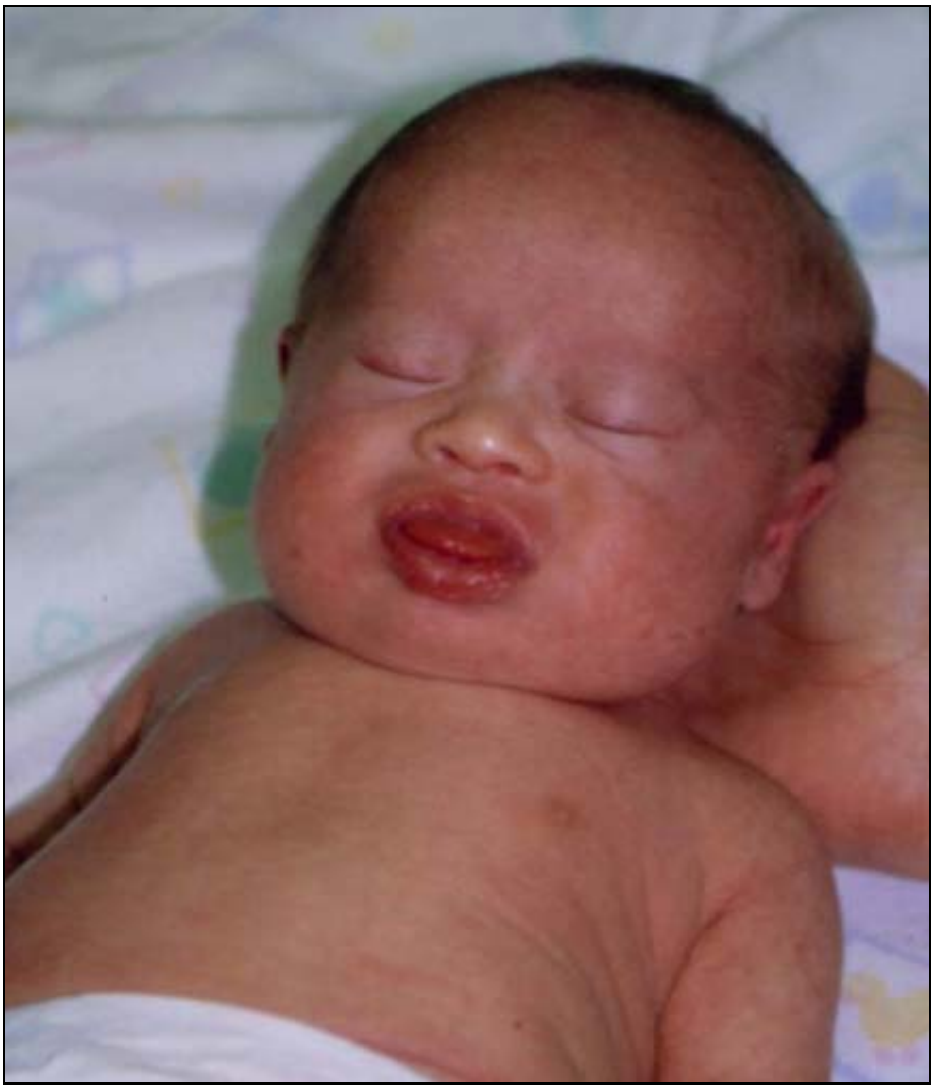
Amniocentesis, routinely performed at 14-16 weeks' gestation, remains the criterion standard of invasive diagnostic tests. Testing for chromosomal disorders is 99.5% accurate. Rare cases of mosaicism are missed, and results can be inaccurate if maternal-cell contamination occurs. The procedure is associated with a small risk of pregnancy loss (1:200-300).

CVS is performed at 10-13 weeks' gestation. Testing earlier than this is thought to be associated with a 1 in 300-1000 risk of fetal transverse limb deficiency, a small risk of maternal cell contamination, and a 0.5-1% risk of a fetal loss after the procedure. The accuracy (96-98%) is less than that of midtrimester amniocentesis because of confined placental mosaicism and maternal-cell contamination.

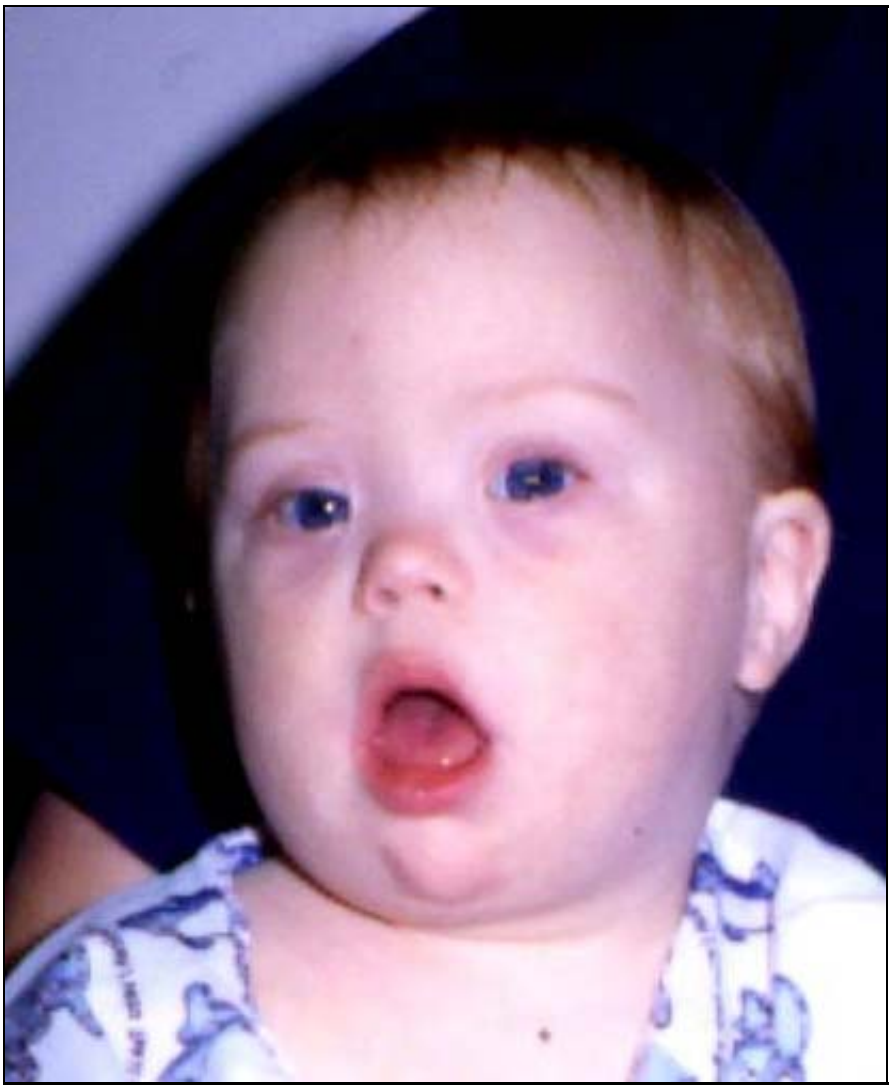
Percutaneous umbilical blood sampling (PUBS) is approximately 95% successful in obtaining a blood sample for cytogenetic testing. The pregnancy-loss rate is 3.25% for PUBS done for chromosomal indications versus 1.25% and 2.75% for PUBS done for nonchromosomal indications. The indication for the procedure greatly increases the risk of procedure-related pregnancy loss.

The availability of in vitro fertilization has allowed for preimplantation diagnosis of single-gene disorders, for sex selection for X-linked disorders, and for identifying chromosomal aneuploidies. After a biopsy sample is obtained from the first polar body, the blastocyst, or the 6-cell to 8-cell embryo, FISH can then be used to diagnose fetal aneuploidy. However, standard cytogenetic confirmation is not possible for the preimplantation diagnosis.

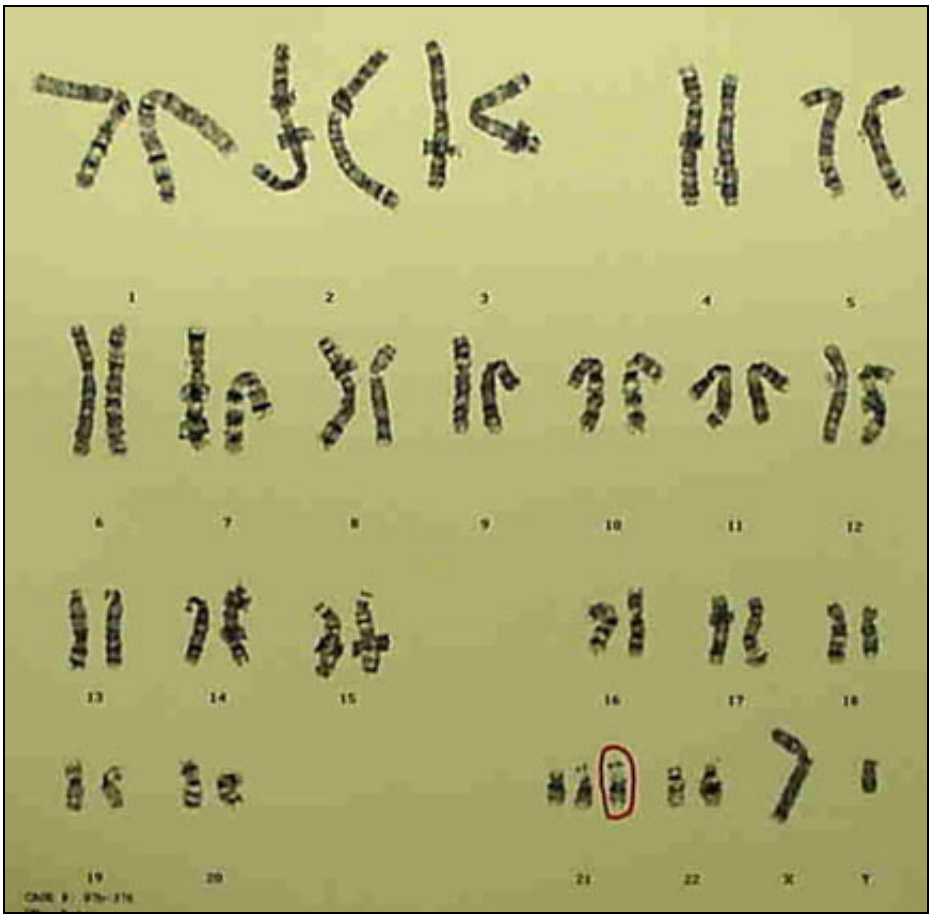
Multimedia



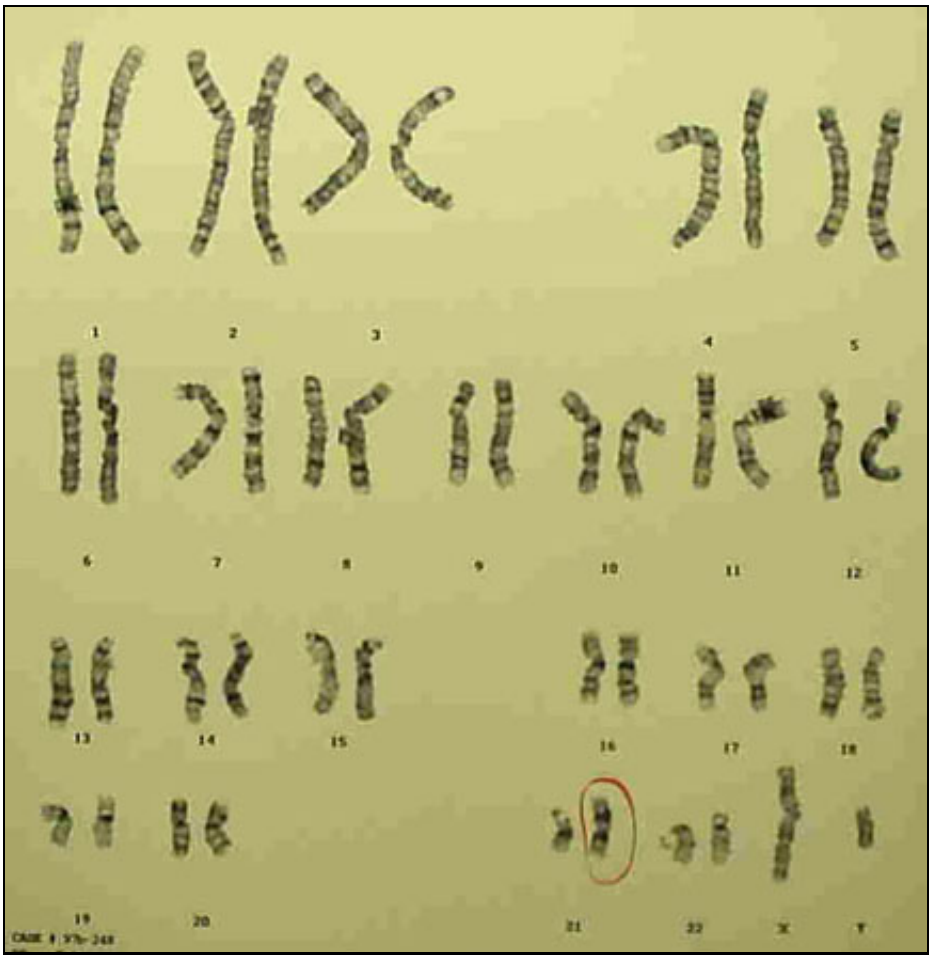
Media file 1: Infant with Down syndrome. Note up-slanting palpebral fissures, bilateral epicanthal folds, flat nasal bridge, open mouth with tendency of tongue protrusion, and small ear with overfolded helix.



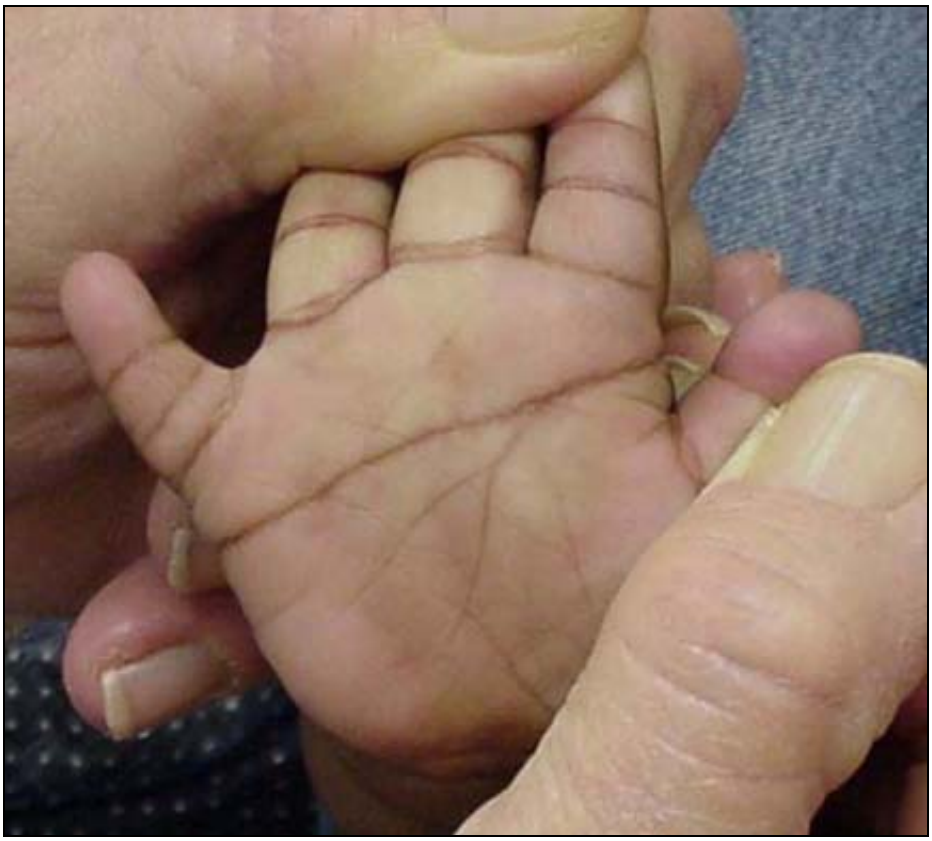
Media file 2: Child with Down syndrome. Note up-slanting palpebral fissures, bilateral epicanthal folds, a small nose with flat nasal bridge, open mouth with tendency for tongue protrusion, and small ears with overfolded helix.



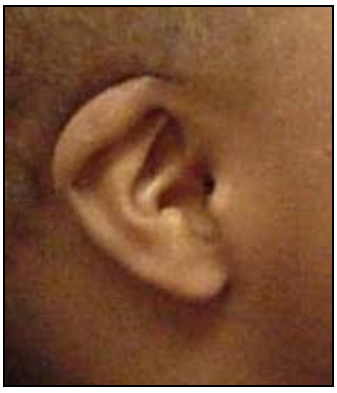
Media file 3: G-banded karyotype showing trisomy 21 (47,XY,+21).



Media file 4: G-banded karyotype showing trisomy 21 of isochromosome arm 21q type [46,XY,i(21)(q10)].



Media file 5: Hand of an infant with Down syndrome. Note the transverse palmar crease and clinodactyly of the 5th finger.



Media file 6: Ear of an infant with Down syndrome. Note the characteristic small ear with overfolded helix.

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