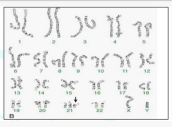
Down Syndrome (Trisomy 21)

Definition & Epidemiology

- Down syndrome (DS) is the most common abnormality of chromosomal number in liveborn infants.
- It is caused by the presence of all or part of a third copy of chromosome 21.
- It is the most common genetic cause of mental retardation.
- Incidence: Approximately 1 in every 700 births.

Risk Factors

- Advancing maternal age (usually ≥35 years).
- Mother who already has one child with Down syndrome (↑ risk in subsequent pregnancies).
- Consanguinity.
- Region of residence.
- Exposure of parents to drugs.
- Educational status of parents.
- Habits of the father.
- Prenatal (antenatal) scanning.
- Reproductive performance of mothers.



Etiology / Genetic Mechanisms

1. Nondisjunction (95%)

- Accounts for most cases (95%) of Down syndrome.
- Usually occurs during maternal meiosis phase I.
- Leads to three copies of chromosome 21 (Trisomy 21) in the fertilized egg.
- Karyotype:
  - 47, XX, +21
  - 47, XY, +21

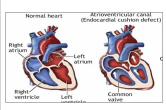
2. Robertsonian Translocation

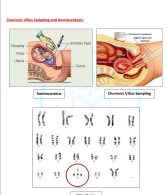
- Most common Robertsonian translocation involves chromosomes 14 and 21.
- Karyotype:
  - 46, XX, t(14q21q)
  - 46, XY, t(14q21q)

3. Mosaic Trisomy 21

- Two cell populations:
  - One with trisomy 21.
  - One with normal chromosome complement.
- Clinical features show wide variation.
- Often milder, but severity is variable.
- Karyotype:
  - 47, XX, +21 / 46, XX
  - 47, XY, +21 / 46, XY

Clinical Features





Systemic associations

CNS Manifestations

- Hypotonia → explains gross motor delay.
- Poor Moro reflex.

CVS manifestation

Congenital Heart Defects (≈50%)

- Endocardial cushion defect (43%).
- Ventricular septal defect (32%).
- Atrial septal defect (10%).
- Tetralogy of Fallot (6%).
- Isolated PDA (4%).
- Acquired valve regurgitation in adults.
- Endocarditis.
- Aberrant subclavian artery.

Endocardial Cushion Defect

- Most common cause of death in infants with DS.

Symptoms

- Difficult breathing.
- Poor feeding.
- Excessive sweating.
- Cyanosis.

Signs

- Arrhythmia.
- Tachypnea.
- Pulmonary hypertension.

Diagnosis

- Echocardiogram after birth.
- ECG.

Treatment

- Surgical correction.

Pulmonary Complications

- Recurrent infections.
- Sleep-disordered breathing.
- Tracheobronchomalacia.
- Tracheal bronchus.
- Pulmonary hypertension.
- Asthma.

Gastrointestinal Abnormalities

- 5–10% of newborns affected.
- Intestinal obstruction → Double bubble sign.
- Common defects:
  - Duodenal atresia.
  - Annular pancreas.
  - Imperforate anus.
- Hirschsprung disease.
- Tracheoesophageal fistula.
- Neonatal cholestasis.
- Increased risk of celiac disease.

Musculoskeletal

- Joint hyperflexibility.
- Pelvic dysplasia.
- Short sternum.
- Atlantoaxial instability:
  - Increased distance between C1 and C2.
  - Risk of spinal cord injury (~15%).

Psychosocial

- Increased risk of behavioral problems.
- Psychiatric comorbidity: 18–38%.
- Responsive to educational, behavioral, and pharmacologic interventions.
- Adults can perform daily activities.
- Difficulty with complex decisions → may require guardian.

Endocrine Disorders

Hypothyroidism

- Congenital hypothyroidism: 18%.
- Acquired hypothyroidism more common in adults.
- Thyroid monitoring:
  - 6 months.
  - 12 months.
  - Annually thereafter.
- Associated symptoms:
  - Fatigue.
  - Mental sluggishness.
  - Weight changes.
  - Irritability.

Diabetes

- Type 1 diabetes most common in children.
- Type 2 diabetes may also occur.
- Others:
  - Obesity.
  - Infertility.
  - Hyperthyroidism.

Hematologic Disorders

- Leukemia risk increased 10–20 fold.
- <2 years: Acute megakaryoblastic leukemia (AML).
- 3 years: Acute lymphoblastic leukemia (ALL).
- Leukemia accounts for 97% of cancers in DS.
- Solid tumors are rare.
- Polycythemia at birth:
  - Hematocrit >70%.
  - Often associated with cardiac defects.

Characteristic features

1. Head and Neck

Skull

- Delayed closure of anterior fontanelle.
- Fine, silky hair.
- Microcephaly.
- Brachycephaly with flat occiput.

Neck

- Short and broad neck.
- Increased nuchal ("nape") skin.

2. Face

Eyes

- Upward slanting palpebral fissures.
- Hypertelorism.
- Epicanthic folds.
- Brushfield's spots.

Nose

- Flat nasal bridge.

Oral Cavity

- Protruded tongue with open mouth.
- Deep furrowed tongue.
- Drooling.
- Short hard palate.

Ears

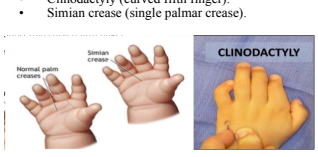
- Small size.
- Low-set ears.
- Overfolded helix.

Other Facial Features

- Midfacial hypoplasia.
- Frontal sinus hypoplasia.

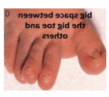
3. Upper Limbs

- Brachydactyly (short fingers/toes).
- Clinodactyly (curved fifth finger).
- Simian crease (single palmar crease).



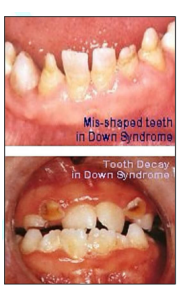
4. Lower Limbs

- Wide gap between first and second toes (sandal gap).



5. Stomatologic Findings

- Delayed eruption of deciduous and permanent teeth.
- Abnormal sequence and positioning of teeth.
- Rounded, pointed, or cone-shaped teeth.
- Small teeth with spacing.
- Fewer teeth.
- Narrow maxilla.
- Tongue appears large for mouth.
- Mouth breathing leading to:
  - Dry mouth and lips.
  - Fungal infections.
  - Ulcers.
  - Gum problems.



Growth and Development

General Growth

- Delayed growth measurements.
- Delayed motor development.
- Delayed mental development.

Developmental Characteristics

- Developmental delay is universal.
- Children have their own developmental milestones.
- Fine motor skills lag behind gross motor skills.
- Social development often relatively spared.
- Autism spectrum disorder may occur.
- Language:
  - Better understanding than expression.

Developmental Milestones

- Delayed across all domains.

Milestone	CHILDREN WITH DOWN SYNDROME		UNAFFECTED CHILDREN	
	Average (mo)	Range (mo)	Average (mo)	Range (mo)
Smiling	2	1.5-3	1	1.5-3
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.

Self-Help Skills

- Delayed but achievable with support.

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.

Mental Retardation

- Intellectual disability:
  - Mild: IQ 50–70
  - Moderate: IQ 35–50
- Speech delay:
  - Expressive speech delay > receptive delay

Increased Susceptibility To

Visual

- Cataracts.
- Nystagmus.

Hearing

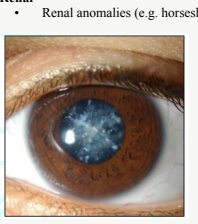
- Recurrent otitis media.
- Congenital or acquired hearing loss.

Neuropsychiatric

- Developmental delay.
- Seizures.
- Autism spectrum disorder.
- Behavioral disorders.
- Depression.
- Alzheimer disease.

Renal

- Renal anomalies (e.g. horseshoe kidney).



Approach (Triple Assessment)

History

- Maternal age.
- Family history.
- Antenatal care.
- Postnatal history:
  - NICU admission.
  - RDS.
  - Jaundice.

Physical Examination

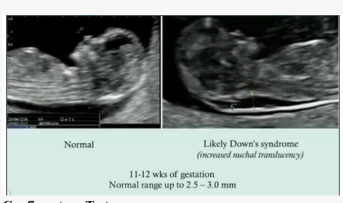
- General examination.
- Growth parameters (DS growth charts).
- Developmental assessment (DS milestones).
- Vital signs.

	Down Syndrome
AFP (Alpha Fetoprotein)	Low
hCG (Human Chorionic Gonadotropin)	High
Ue3 (Unconjugated Estriol)	Low
Inhibin A	High

Diagnostic Tests

Prenatal Screening

- First trimester:
  - Nuchal translucency (NT):
    - NT alone detects ≤70%.
    - NT + biochemical markers → up to 95%.
- Second trimester:
  - Biochemical markers.

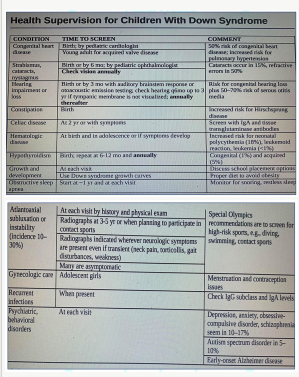


Confirmatory Tests

- Chorionic villus sampling.
- Amniocentesis.
- Karyotype analysis.

Management

- No specific cure.
- Regular follow-up.
- Special education.
- Medical management of heart failure.
- Surgical correction of cardiac and GI defects.
- Monitor vision.
- Monitor for leukemia.
- Growth monitoring on DS growth charts.
- Annual hearing assessment.



Edward's Syndrome (Trisomy 18)

Definition & Epidemiology

- Trisomy 18.
- Karyotype:
  - 47, XX, +18
  - 47, XY, +18

- Second most common autosomal trisomy.
- Occurs in approximately 1 in 7,500 live births.

Survival & Prognosis

- Infants with trisomy 18 rarely survive.
- More than 95% are lost as spontaneous abortions in the first trimester.
- Females are more likely to survive to term than males.
  - Female : Male ratio = 1 : 4

- Fewer than 10% survive to their first birthday.

Clinical Features

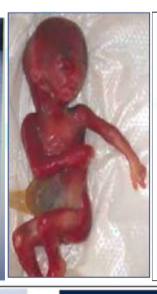
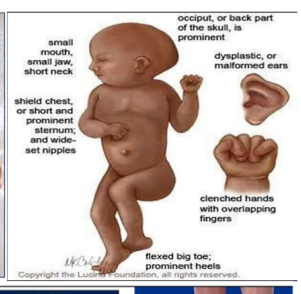
General
- Hypertonia.
- Small for gestational age.

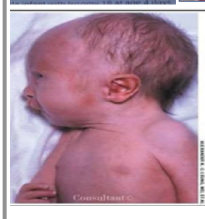
Head
- Prominent occiput.
- Micrognathia.
- Low-set and malformed ears.

Limbs
- Clubfeet.
- Rocker-bottom feet.
- Clenching of fists:
  - Second and fifth digits overlap the third and fourth digits.
-
- Hypoplastic nails.

Heart
- Congenital heart disease:
  - Ventricular septal defect (VSD).
  - Patent ductus arteriosus (PDA).
  - Atrial septal defect (ASD).

Chest
- Short sternum.
- Small nipples.



Trisomy 13 (Patau Syndrome)

Definition & Epidemiology

- Least common but most severe trisomy.
- Prevalence: 1 in 5,000 newborns.
- Majority of prenatally diagnosed cases die in utero.
- Median survival of liveborn children: 7 days.
- 91% die within the first year.
- Approximately 80% die within the first month of life.

Etiology

- Most commonly due to nondisjunction.
- Can also be due to:
  - Robertsonian translocation.
  - Mosaicism.

Major Risk Factors

- Advancing maternal age.
- Family history.

Diagnosis

Prenatal Screening

- Ultrasound:
  - Increased nuchal translucency.

- Serum markers:
  - Low HCG.
  - Low PAPP-A.

Confirmatory Test

- Karyotyping.

Treatment

- No known cure.
- Supportive management only.

Clinical Presentation

1. Mental Retardation
- Severe intellectual disability.

2. Growth Retardation
- Prenatal growth deficiency.
- Postnatal failure to thrive (if survival occurs).

3. Physical Findings

Head
- Microcephaly.
- Sloping forehead.
- Cutis aplasia.
- Cyclopia.
- Proboscis.

Eyes
- Micropthalmia.
- Anopthalmia.

Mouth / Oral Cavity
- Absent philtrum.
- Cleft lip or palate.
- Narrow palate.
- Micrognathia.

Ears
- Small, malformed ears.

Upper Limbs
- Polydactyly.
- Hypoplastic nails.

Lower Limbs
- Polydactyly.
- Rocker-bottom feet.
- Capillary hemangiomata.

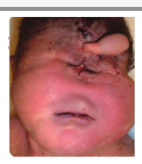
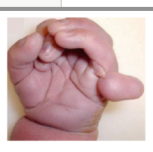
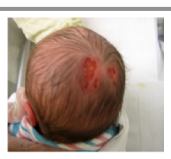
4. Systemic Associations

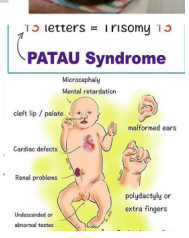
Central Nervous System (CNS)
- Holoprosencephaly.
- Meningomyelocele.
- Cerebral hypoplasia.
- Agenesis of corpus callosum.

Cardiovascular System (≈80%)
- Ventricular septal defect (VSD).
- Atrial septal defect (ASD).
- Patent ductus arteriosus (PDA).
- Dextrocardia.

Gastrointestinal System
- Omphalocele.
- Malrotation of the gut.
- Meckel diverticulum.

Renal & Genitourinary
- Horseshoe kidney.
- Polycystic kidney disease (PCKD).
- Hydronephrosis.
- Cryptorchidism.
- Bicornuate uterus.

Klinefelter Syndrome

Definition & Epidemiology

- Klinefelter syndrome is a chromosomal condition affecting male physical and cognitive development.
- Normal male karyotype: 46, XY.
- In Klinefelter syndrome there is at least one extra X chromosome (XXY).
- Most common human sex chromosome disorder.
- Prevalence: 1 in 500 males.
- Most common chromosomal disorder associated with:
  - Male hypogonadism.
  - Infertility.

- No characteristic congenital heart disease in Klinefelter syndrome.

Etiology

- Not inherited.
- Caused by nondisjunction during cell division.
- An egg or sperm cell gains one or more extra X chromosomes.
- If this abnormal gamete contributes to fertilization, the child will have extra X chromosomes in all cells.

Mosaic Klinefelter Syndrome
- Karyotype: 46, XY / 47, XXY.
- Not inherited.
- Some cells are normal (46, XY).
- Other cells have an extra X chromosome (47, XXY).

Presentation

History / Symptoms

- Hypogonadism.
- Gynecomastia.
- Infertility.
- Taller than peers.
- Delayed or incomplete pubertal development.
- Sparse facial, body, and sexual hair.
- Erectile dysfunction.
- Osteoporosis.
- Increased risk of:
  - Breast malignancy.
  - Chronic inflammatory diseases (e.g. SLE).

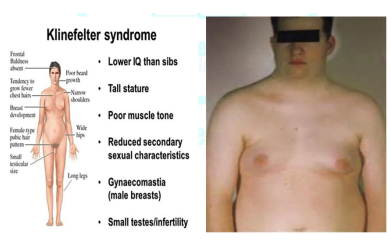
- Speech and language deficits:
  - Especially expressive language.

- Learning disabilities:
  - Lower verbal IQ compared to performance IQ.

- Poor self-esteem.
- Increased incidence of:
  - Anxiety.
  - Depression.

- Behavioral problems:
  - Substance abuse.

Hormonal Findings
- Low testosterone.
- High estrogen : testosterone ratio.



Laboratory Studies

Prenatal Testing

- Fetal cytogenetic analysis:
  - Chorionic villi.
  - Amniocytes.

- Noninvasive prenatal testing (NIPT):
  - Analysis of cell-free fetal DNA in maternal blood.

Postnatal Testing

- Diagnosis is often clinically age-related.
- Karyotype analysis.
-

Treatment

Androgen Replacement Therapy

- Most important aspect of treatment.
- Started at puberty.
- Dose increased gradually over time.
- Results in:
  - Deeper voice.
  - Growth of facial and body hair.
  - Increased muscle mass.
  - Increased penis size.

- Does not:
  - Enlarge testicles.
  - Improve infertility.

Other Treatment

- Breast tissue removal:
  - For gynecomastia.
  - Due to increased risk of breast cancer.

- Speech and behavioral therapy.
- Physical and occupational therapy:
  - For hypotonia.

- Psychological counseling.

Treatment of Infertility

- Isolation of viable sperm via testicular biopsy.
- Combined with:
  - In vitro fertilization (IVF).
  - Intracytoplasmic sperm injection (ICSI).

- Allows some men with KS to father children.

Turner Syndrome (45, XO)

Definition & Epidemiology

- Genetic condition affecting only females.
- One X chromosome is missing or structurally altered.
- Karyotype: 45, XO.
- The only monosomy compatible with survival to term.
- Incidence: 1 in 3,200 live-born females.
- Advanced maternal age is not associated.
- Not inherited:
  - Women with Turner syndrome are usually sterile.

Etiology

- Typically caused by nondisjunction of sex chromosomes during meiosis.

Karyotype Variations
- Classical monosomy X (45, XO): 50%.
- Mosaic (45, XO / 46, XX): 30–40%.
- Structural defect of X chromosome (partial deletion): 10–20%.

Presentation

General Features
- Short stature.
- Cystic hygroma.
- Webbed neck.
- Triangular face.
- Drooping eyelids.
- Low-set ears.
- Puffiness of hands and feet (lymphedema).
- Shield chest with widened internipple distance.
- Cubitus valgus.

Cardiovascular System

- Most common:
  - Coarctation of the aorta.

- Second most common:
  - Bicuspid aortic valve.

- May cause lower extremity cyanosis.

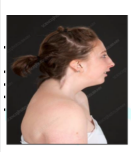
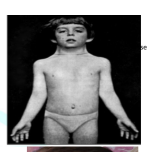
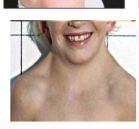
Renal
- Horseshoe kidney.

Musculoskeletal System
- Osteoporosis (due to lack of estrogen).

Endocrine
- Hypothyroidism.
- Type 2 diabetes.

Gonadal
- 95% have:
  - Gonadal failure.
  - Streak ovaries.

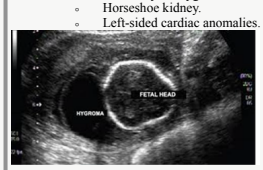
- Results in:
  - Estrogen deficiency.
  - Failure to develop secondary sexual characteristics.
  - Primary amenorrhea.


Laboratory Studies

Prenatal Diagnosis

- Amniocentesis.
- Chorionic villous sampling.
- Fetal ultrasonography findings:
  - Nuchal cystic hygroma.
  - Horseshoe kidney.
  - Left-sided cardiac anomalies.



Postnatal Diagnosis

- Karyotype analysis.

Laboratory Studies

- Gonadotropins:
  - LH and FSH elevated in untreated patients younger than 4 years.

- Fasting blood glucose.
- Thyroid function tests.
- Echocardiography.
- Limb blood pressure measurements.

Treatment

- Growth hormone therapy (childhood):
  - Standard treatment to prevent short stature.

- Sex hormone replacement therapy (adolescence):
  - Estrogen usually started at 12–15 years.

- In vitro fertilization (IVF):
  - Can make pregnancy possible.

Prader–Willi Syndrome

General Information

- Non-inherited disorder.
- Occurs sporadically.
- Most common genetically identified cause of life-threatening obesity.
- Prevalence: 1 in 12,000–15,000.
- Affects both sexes and all races.

Genetics

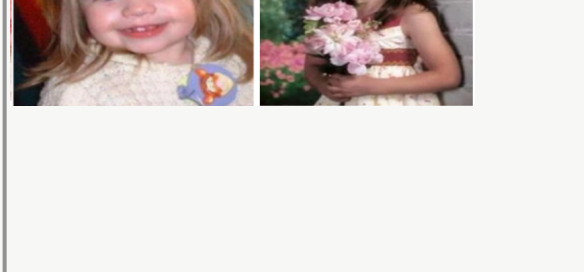
- Disorder of chromosome 15.
- Region involved: 15q11.2–13.

Developmental Concerns

- Hypotonia in infancy:
  - Improves with age.
  - May cause feeding difficulties.
  - Associated with delayed speech.
- Deficits in:
  - Strength.
  - Coordination.
  - Balance.
- Intelligence:
  - IQ range: 40–105.
  - Average IQ: 70.
- Individuals with normal IQ:
  - Usually have learning disabilities.

Physical Features

- Short stature.
- Long and narrow head at birth.
- Narrow face.
- Distinct eyes (almond-shaped).
- Small mouth with downward-curved corners.
- Thin upper lip.
- Small upturned nose.
- Small hands and feet.



Angelman Syndrome

Definition

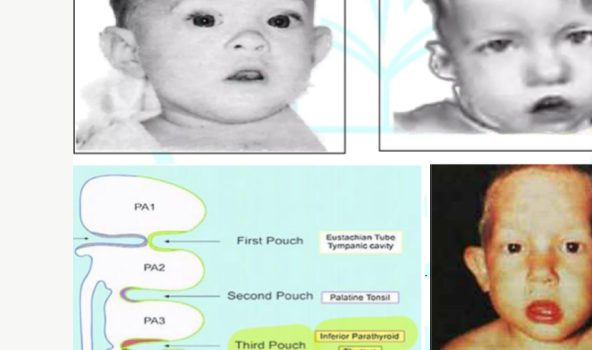
- Genetic disorder causing:
  - Developmental delay.
  - Neurological problems.

Genetics

- Deletion of a region in chromosome 15.
- Absence of a functional copy of the UBE3A gene.
- The missing gene is normally inherited from the mother.

Clinical Features (Symptoms)

- Microcephaly (small head size).
- Hyperactivity.
- Seizures.
- Sleep disorders.
- Balance disorders.
- Frequent laughter and smiling.
- Speech impairment.
- Uplifted, flexed arms.
- Sensitivity to heat.



T Williams Syndrome (Williams–Beuren Syndrome)

Definition & Epidemiology

- Developmental disorder affecting multiple body systems.

Causes

- Deletion of genetic material from chromosome 7.
- Involves deletion of 26–28 genes.
- Includes deletion of the elastin gene.
- Elastin protein:
  - Provides blood vessels with stretchiness and strength throughout life.

Common Features

- Mental retardation.
- Congenital heart defects.
- Unusual facial features.

Other Features

- Low birth weight.
- Failure to gain weight appropriately.
- Kidney abnormalities.
- Low muscle tone.

Behavioral Characteristics

- Hypersensitivity to loud noises.
- Overly outgoing personality.

Management

Treatment

- No cure for Williams syndrome.
- Avoid calcium and vitamin D supplementation:
  - Risk of blood vessel narrowing.

DiGeorge Syndrome (CATCH 22 Syndrome)

- Autosomal dominant primary immunodeficiency disease.
- Caused by a defect in chromosome 22 at location q11.2.
- Leads to failure of development of the 3rd and 4th pharyngeal arches.
- Incidence: 1 in 4,000 live births.

CATCH 22 Syndrome

- C – Cardiac defects:
  - Truncus arteriosus.
  - Tetralogy of Fallot (TOF).
- A – Abnormal facies:
  - Long face.
  - Hypertelorism.
  - Short palpebral fissures.
  - Fish-like mouth.
- T – Thymic hypoplasia.
- C – Cleft palate.
- H – Hypocalcemia.
- 22 – Refers to chromosome 22.

Surgical Management

- Cardiac anomalies:
  - Require immediate surgical management.
- Craniofacial abnormalities:
  - Corrected based on severity of airflow compromise.

Abnormal Facial Features

Facial features of children with DiGeorge syndrome include:

- Hypertelorism.
- Short palpebral fissures.
- Short philtrum with fish-mouth appearance.
- Micrognathia.
- Low-set ears.
- Telecanthus with short palpebral fissures.

History

- Maternal history:
  - Diabetes.
  - Prenatal exposure to alcohol or drugs (e.g. isotretinoin).
  - Family history.
- Recurrent infections.
- Feeding difficulties.
- Developmental delay.
- Learning difficulties.
- Behavioral and neuropsychiatric problems.
- Endocrinologic manifestations:
  - Hypocalcemia.
  - Tetany.
  - Seizures.

Physical Examination

- Cardiac murmur.
- Facial abnormalities.
- Urogenital malformations.

Genetic Analysis

- Array Comparative Genomic Hybridization (aCGH):
  - Detects 22q11 deletion.
- Karyotyping.
- FISH:
  - Requested if aCGH is unavailable.
- Multiplex ligand binding:
  - For TBX1 deletions.

T-Cell Analysis

- Absolute lymphocyte count in peripheral blood.
- Flow cytometry:
  - CD45RA+ T cells.
  - CD45RO+ T cells.
- RT-PCR assay.
- Antibody response assessment.

Imaging

- CT and MRI:
  - May show cardiac anomalies.
  - Thymus aplasia or hypoplasia is not visible.
- Echocardiography:
  - Useful for truncal cardiac abnormalities.
- Angiography:
  - Useful for detecting internal carotid artery malformations.