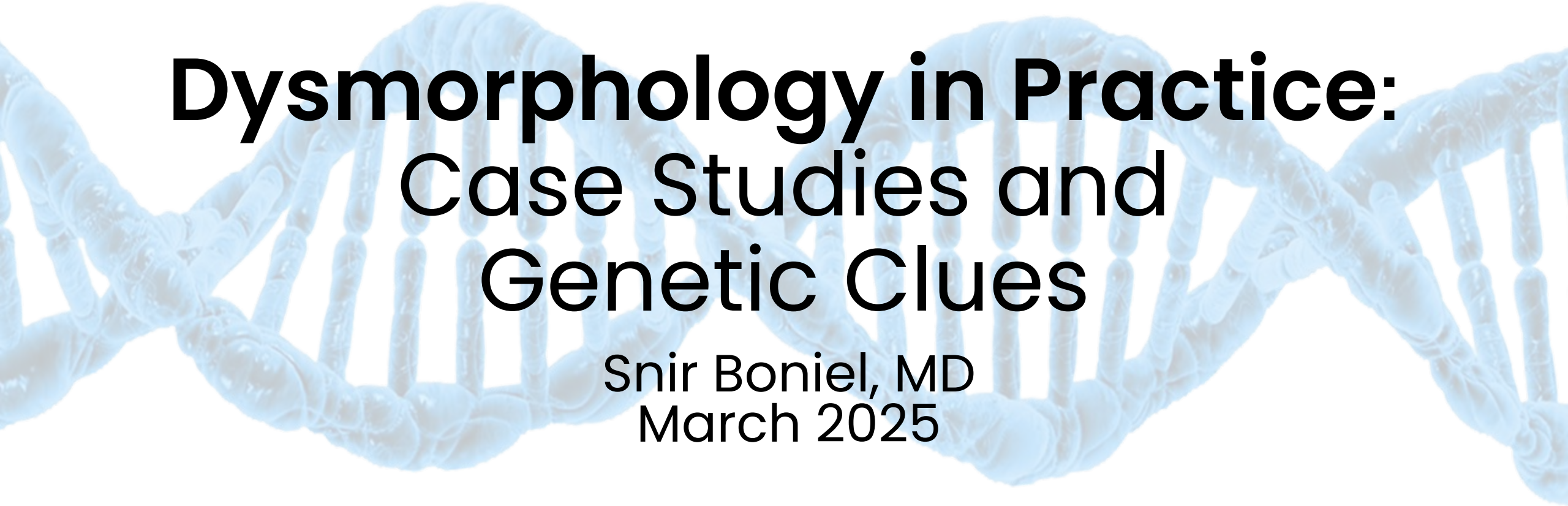

Dysmorphology in Practice: Case Studies and Genetic Clues

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Students will be able to:

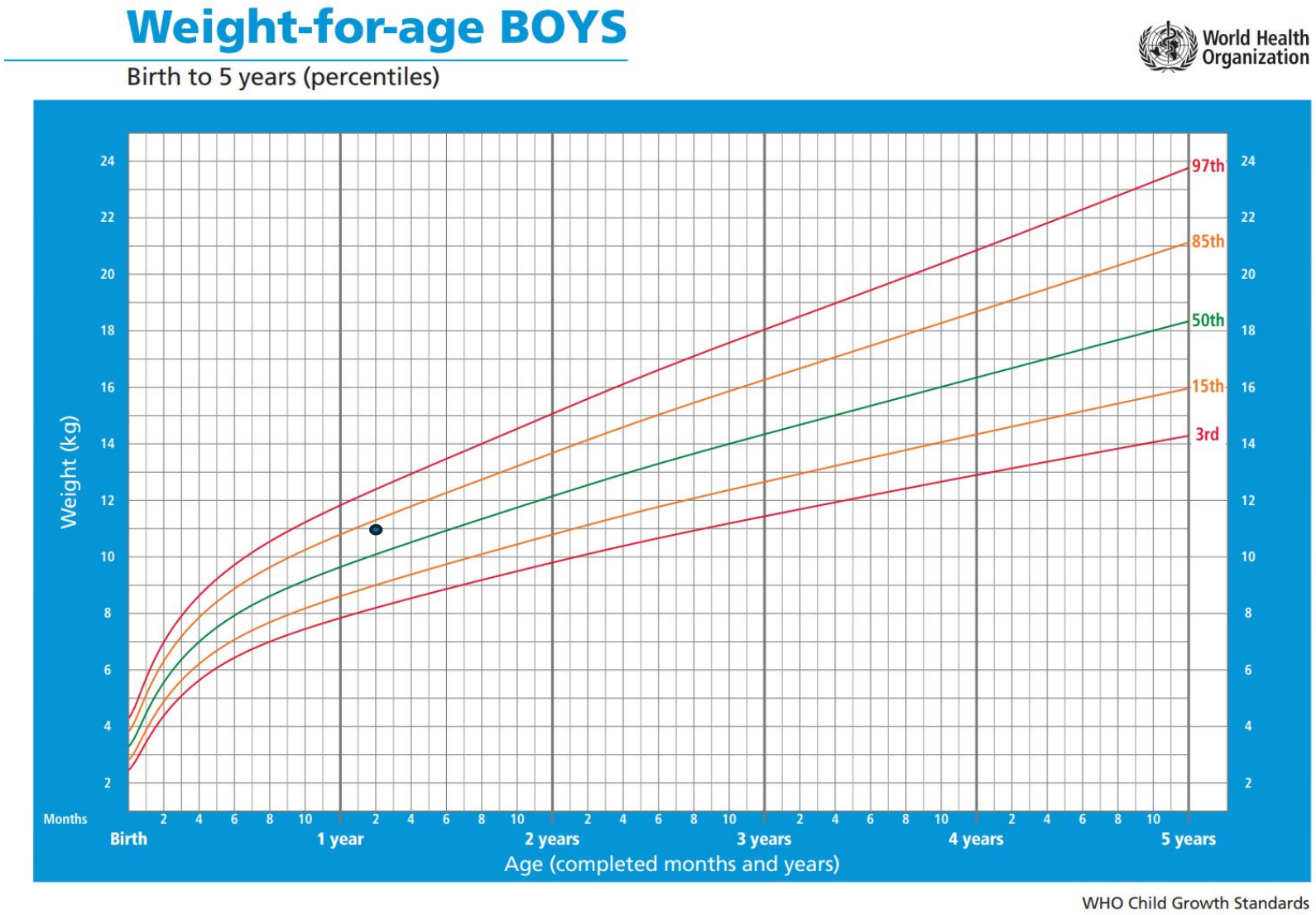
- Recognize and describe dysmorphic features
- Suggest differential diagnoses
- Correlate phenotypes with genotypes
- Review diagnostic tools' role in confirming diagnoses (karyotyping, microarrays, gene sequencing and more)
- Review knowledge from the course (years 2 and 3)

Lesson Plan

- Groups of 3-4
- Each group will receive 2 cases.
- Read the cases, discuss and answer the questions.
- Starting 8:30 – student-led a class discussion

Quick Growth Chart Review

- Example: 14-month-old boy, weight 11kg. What percentile curve does he follow?
- 50-85th.
- Remember: WHO growth charts for healthy children born at term, but there are others!



Case 1

A 5-year-old boy (G1-polyhydramnios, uncomplicated labor and delivery) presents to the Genetics Outpatient Clinic:
He has a history significant for:

- Failure to Thrive
- Psychomotor developmental delay (delayed walking, talking and growth).
- Difficulty feeding, slow weight gain
- Learning disabilities
- Visual impairment and strabismus.
- Hearing loss
- Congenital heart disease

Case 1

Task: Examine the patient and describe the dysmorphism. How did these dysmorphic features develop? Which other physical exam findings do you expect?

- Downslanting palpebral fissures (old terminology: antimongoloid).
- Low-set ears
- Low nasolabial folds
- Drooping mouth corners
- Ptosis
- Webbed neck
- As if you pull the face down. Why does it look like that? What happened prenatally?
- *Noonan syndrome: PTPN11 mutation*

Question 2: What does this diagnosis mean for the patient?

Question 3: Will you refer the patient to other specialists? If so, which ones?

Case 1: MCQ

Which syndrome shares the most phenotypic similarities with Noonan syndrome?

A. Wolff-Hirschhorn syndrome
B. Turner syndrome
C. Cornelia de Lange syndrome
D. Ehlers-Danlos syndrome

Case 2

A 3-year-old boy is brought to the pediatrician by his parents, who are primarily concerned about his tendency to bruise easily. They report finding new bruises on his body almost every time he plays outside. He had a prolonged bleeding episode lasting several hours following a routine oral cleaning procedure during his first dental check up. Upon further questioning, they mention that he occasionally passes blood in his urine and sometimes experiences nosebleeds. Physical examination findings are unremarkable, although you note that he is circumcised. The parents casually mention that he was circumcised as a newborn and that he bled from the wound for several hours after the procedure, and even ultimately required treatment in the emergency department.

Case 2

Question 1: What is your suspected differential diagnosis?

- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)
- Other coagulopathy

Question 2: How will you confirm your diagnosis?

- CBC: PLT normal
- PT: normal.
- PTT: prolonged.
- Specific factor 8 or 9 activities.
- Mutation testing.

Question 3: What does this mean for the patient's family and his future offspring?

- X-linked recessive!

Question 4: Which treatment options do you suggest to the caregivers? Will you refer the patient to other specialists? If so, which ones? What else would you recommend for caregivers?

Case 2: MCQs

A father with Hemophilia A has 3 daughters and 1 son. This means that:

A. the son and all daughters are unaffected.
B. all daughters are carriers and the son is healthy.
C. the son is affected, two of the daughters are carriers.
D. the son is unaffected, two of the daughters are carriers.

	X^h	Y
X	X^hX	XY
X	X^hX	XY

The probability that a female carrier of hemophilia will pass on a mutated X-chromosome to her children is:

A. 25%
B. 50%
C. 75%
D. 100%

	X	Y
X^h	X^hX	X^hY
X	XX	XY

Case 3

A 3-year-old boy presents to the Genetics Outpatient Clinic. He was referred there by a pediatrician due to dysmorphic features, short stature, developmental delay and, according to the referral note, an “abnormal behavioral phenotype.” His parents say that this this boy has an outgoing personality and happily engages with other people.

Case 3

Task 1: Examine the patient and describe the dysmorphism.

- Round face – excess subcutaneous tissue.
- External supraorbital area looks the same
- Thick lips
- Facial feature hypomimia
- Triangular nose
- Elfin face
- Long/misshapen palpebral features

Cleveland Clinic. (n.d.). *Williams syndrome*. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/15174-williams-syndrome

Case 3

Question 1: What is your differential diagnosis? How will you confirm it?

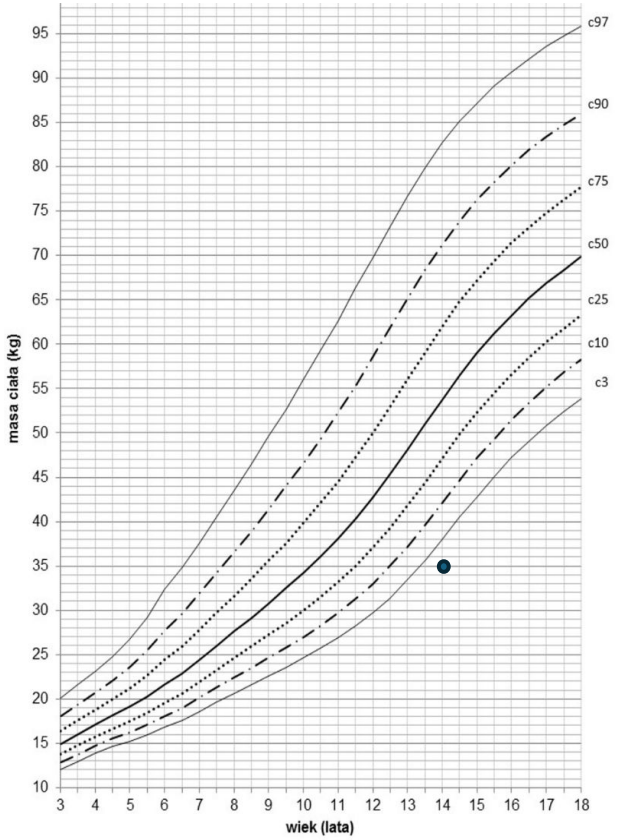
- Chromosomal microarray aCGH.
- Results: arr|GRCh38/hg38|7q11.23(7:72,700,001-77,900,000)x1 .
- Williams Syndrome

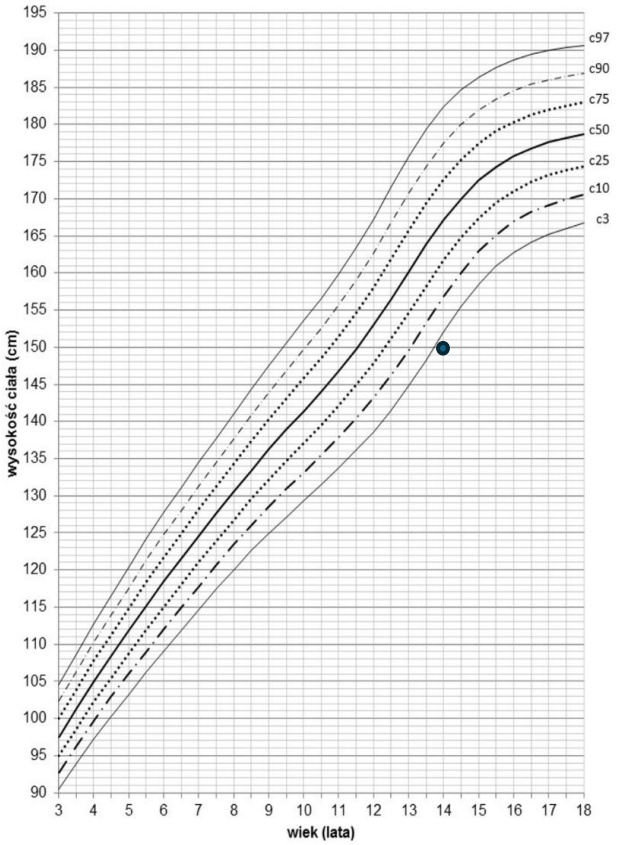
Question 2: Will you refer the patient to other specialists? If so, which ones and why?

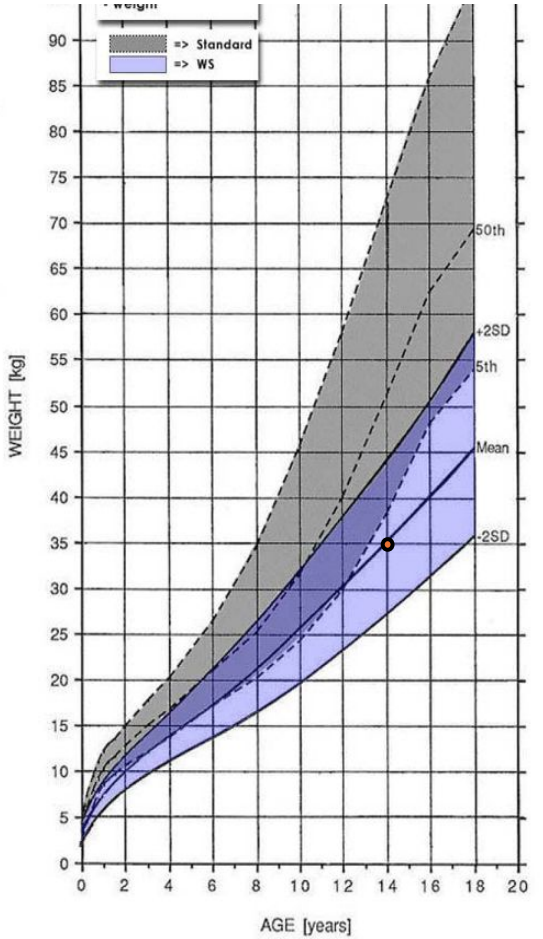
- Connective tissue disorders. Aortic stenosis / defects of aorta.

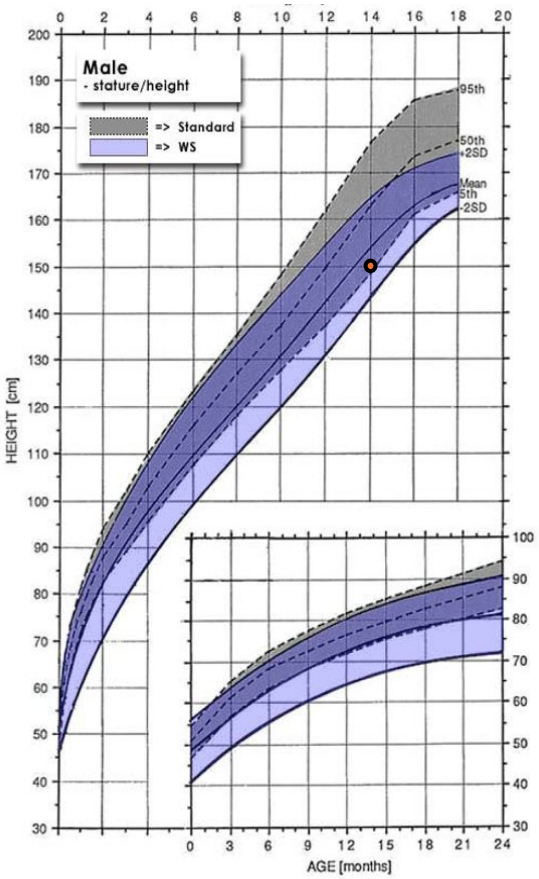
Case 3

Task 2: *Fast-forward a few years*. You see this patient for a follow-up visit at the age of 14 years. You measure his height (150cm) and his weight (35kg).
Please comment on your findings.









Case 4

A 30-year-old woman presents to her family doctor complaining of extreme fatigue. She says she has always felt tired, but in recent years this has become increasingly unbearable. She even feels short-of-breath, especially after exertion.

Besides that, she says that in recent months she's noticed "weird bronze spots" on her face, neck, elbows, groin and knee skin. She complains of generalized joint pain.

She says she hasn't really seen a doctor during her adult life. When prompted, she mentions that "she thinks her mother had something wrong with her blood," but she doesn't remember exactly what.

iCliniq. (n.d.). *Iron overload (Hemochromatosis)*. Native Care. https://nativecare.icliniq.com/articles/blood-health/iron-overload-hemochromatosis

Case 4

Question 1: What is your differential diagnosis? Which tests, if any, would you like to perform?

- CBC with differential
- Microcytic anemia
- Suspect genetic disease – single-gene test *HFE*

Question 2: Which treatment options do you suggest? Will you refer the patient to other specialists? If so, which ones? What else would you recommend for this patient?

- Primary hemochromatosis: phlebotomy, alcohol cessation, avoid iron supplements, erythrocytapharesis, liver transplantation.
- Secondary hemochromatosis: treat underlying disease, consider chelating agents (deferoxamine).

Case 4: MCQ

The most common symptom of hemochromatosis is:

A. Joint pain
B. Fatigue
C. Decreased libido
D. Skin hyperpigmentation

Case 5

A 3-month-old infant presents to the pediatric clinic.

Task 1: Examine the patient and describe the dysmorphism.

- Low-set ears
- Micrognathia (small jaw)
- Glossoptosis (downwardly replaced or retracted tongue)
- Cleft palate (not seen)
- *Pierre-Robin sequence disease*

Question 1: What chief concerns does this do your findings mean for the patient? What therapy options would you recommend?

- Upper airway obstruction & feeding difficulties
- Nasogastric tube or PEG feeding, surgical consult.

Case 5

Fast-forward: The patient is 8 years old.

Task 2: Examine your patient and describe the dysmorphism.

- Microtia (small ears)
- Micrognathia (small jaw)
- Glossoptosis (downwardly replaced or retracted tongue)

You note that the boy's knees look strange, so you order an X-ray.

Task 3: Comment on the X-ray image.

- Patellar hypoplasia!! (He's got no kneecaps!)

Case 5

Question 2: What is your differential diagnosis? How will you confirm your diagnosis?

- Cause isn't yet fully understood
- Can be isolated or part of a syndrome, (e.g. Stickler syndrome)
- Array CGH: 17q24.3-q25.1del

Question 3: What will you recommend for this patient's caregivers?

- Airway + Feeding!!
- Mild cases resolve on their own.
- Severe cases surgery.

Case 5: MCQ

A newborn presents with a small mandible, cleft palate, and a tongue displaced posteriorly in the oral cavity. He has respiratory distress with cyanosis and feeding difficulties. The described abnormalities and symptoms are characteristic of:

A. Potter Syndrome
B. Laryngotracheomalacia
C. Fetal alcohol syndrome
D. Pierre Robin sequence

Case 6

A 1-year-old girl presents to the Medical Genetics outpatient clinic. She was referred here by her pediatrician after seeing numerous specialists:

- She underwent a successful cardiosurgical correction of Tetralogy of Fallot during early infancy.
- She is immunodeficient.
- Her serum Ca concentration is chronically around 7,8mg/dL.

Case 6

Task: Describe the dysmorphism you see. Which other abnormalities do you expect in this patient
(hint: not all are visible in this picture).

- Small mouth
- Tubular nose
- Lots of neck tissue
- Hypotonia
- Cardiac defects (ToF, truncus arteriosus, others…)
- Cleft palate
- Thymic aplasia
- Hypoparathyroidism

Case 6

Question 1: What is your suspected differential diagnosis?

- DiGeorge Syndrome!

Question 2: Why is she immunodeficient?

- Thymic aplasia!

Question 3: Comment on those serum calcium levels. Why are they like that?

- Hypoparathyroidism

Case 6: Let's review *Catch-22*

- **C**left palate
- **A**bnormal face
- **T**hymic aplasia
- **C**ardiac defects
- **H**ypocalcemia (hypoparathyroidism)
- **22q11del**

MCQs are literally about that…

Case 7

A 1-day-old newborn was born in critical condition and is currently hospitalized in the NICU due to cardiopulmonary insufficiency. The mother is an undocumented immigrant, has a significant language barrier with the medical staff, and carries no medical records from her pregnancy. The father is not known. At the NICU, you find out that other consulting physicians suspect the baby has serious cardiac and CNS defects. The baby is still undergoing diagnostic tests and results are not yet conclusive. You, the clinical geneticist are called in for a consult:

Case 7

Task: Describe the dysmorphism.

- Cleft palate (unilateral or bilateral?)
- Microcephaly (unclear in photo)
- Nasal anomaly (why?)
- Facial anomaly
- Polydactyly / hexadactyly.

Case 7

Question 1: What is your differential diagnosis? What are the implications of this diagnosis? What tests will you order to confirm this diagnosis?

- Patau syndrome
- 90% die within 1st year of life.
- Otherwise, severe disability, even after surgical intervention
- Karyotyping – Trisomy 13

Question 2: How will you follow-up this diagnosis? Are there any other questions you have for the caretaker, or any information you'd like to tell her? Open ended.

Williams GM, Brady R. Patau Syndrome. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538347/

Case 7: MCQ

Mark the false statement pertaining to Patau syndrome:

A. It is usually a lethal diagnosis.

B. Characteristic traits include microcephaly, congenital heart disease, kidney cysts, and developmental delay.

C. 50% of patients die within the first month of life, and 80-90% within the first year of life.

D. It is a trisomy of chromosome number 21.

Case 8

A 7-year-old boy presents to the Genetics Outpatient Clinic. He was referred here by his pediatrician after seeing numerous specialists. His history is significant for global hypotonia and feeding difficulties during the first year of life. During his second year of life he suffered from recurrent otitis media and currently has suspected hearing loss. Since then, his chief complaint has been developmental psychomotor and speech delay as well as epilepsy. He regularly visits a pediatric neurologist, at this point no chronic treatment is indicated.

Upon physical examination you notice several dozen skin discolorations (his mom says she thinks he's had them since birth but she never really thought about it), some strange growths on several places on his skin, including between his fingers.

Case 8

Task: List three differential diagnoses based on these clinical details.

Question: What additional findings (such as dysmorphic features, genetic test results, or other relevant details) would support each of your differential diagnoses?

- Tuberous Sclerosis
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Others? Sturge-Weber, Von Hippel-Lindau…
- Recurring themes…

Case 8

Tuberous Sclerosis:

- Inheritance: AD
- Pathophysiology: TSC1 chr 9; TSC2 chr 16. *Genetic heterogeneity*.
  - Ungual fibromas
  - Adenoma sebaceum
  - Tumor suppressor genes

Case 8

- Ash-leaf spots
- Cardiac rhabdomyoma
- Renal angiomyolipoma
- Shagreen patches

Case 8

Neurofibromatosis type 1

- Inheritance: AD
- Pathophysiology: NF1 gene (chr17)
- Other findings & characteristics:
  - Axillary hyperpigmentation
  - Risk of pheochromocytoma
  - Scoliosis
  - Risk of Wilm's Tumor
  - Boney involvement
  - Cafe au lait spots
  - cutaneous neurofibromas
  - optic gliomas
  - Lisch nodules

Case 8

Neurofibromatosis type 2

- Inheritance: AD
- Pathophysiology: NF2 tumor suppressor gene (chr22)
- Findings:
  - CN8 – tinnitus & sensorineural hearing loss
  - CN7 – facial paralysis
  - CN5 – facial paresthesia
  - Bilateral acoustic Schwannomas
  - Tumor at the *cerebellopontine angle*

Case 8

Our case?

- Global hypotonia & poor feeding = any
- Recurrent AOM / hearing loss = NF2 (potential ear disease)
- Epilepsy = TS, NF1
- Skin discolorations = TS, NF1
- Strange growths = TS

Case 8: MCQ

Which of the following syndromes may be associated with an increased risk of malignancy?

1. Neurofibromatosis type 1
2. Neurofibromatosis type 2
3. Tuberous sclerosis
4. Von Hippel-Lindau disease
5. Sturge-Weber disease

The correct answer is:

A. 1, 2
B. 2, 3, 4, 5
C. 3, 4
D. All of the above

Case 9

A 3-day-old female newborn is admitted to the neonatal intensive care unit due to respiratory distress and poor feeding. She was born at 37 weeks via emergency C-section due to fetal distress. Her birth weight was 2200g. On examination, a cardiac murmur is noted. Echocardiography revealed a ventricular septal defect. The NICU team observed episodes of apnea and bradycardia.

Case 9

Question 1: Based on the clinical presentation and the image provided, what dysmorphic features do you notice, and how might they guide your differential diagnosis?

- Club foot?
- No…the opposite. Rocker-bottom feet.
- Arthrogryposis – fingers 2&5 cross over 3&4.
- Palpebral fissure deformity. Ocular deformity.
- *Edwards Syndrome (Trisomy 18)*

Case 9

Question 2: What genetic testing would you order to confirm your suspected diagnosis, and what result would you expect?

- Karyotyping. 47,XX,+18.

Question 3: What are the key considerations in counseling the parents regarding prognosis and management options for this condition? Open ended.

Case 9: MCQ

One method for diagnosing chromosomal aberrations is array Comparative Genomic Hybridization (aCGH). Which of the following chromosomal abnormalities cannot be detected using this technique?

A. Turner syndrome

B. Balanced translocation t(11;22)

C. DiGeorge syndrome

D. Edwards Syndrome (trisomy 18)

Case 10

A 10-year-old girl presents to a pediatric neurologist with progressive bilateral leg and ankle weakness, numbness, and tingling. She has been wheelchair-bound for the last two months. Symptoms began in July 2024 at summer camp and were initially thought to be due to intense physical activity. Weakness had worsened by March of 2025. Her psychomotor and cognitive development were normal during early childhood. On further questioning, her mother mentions that the girl's late grandfather was wheelchair-bound for years but never saw a doctor.

Physical exam reveals bilateral sensory loss in her lower limbs, absent deep tendon reflexes, and leg muscle atrophy. She can only take a few steps and has a steppage gait, lifting her legs high to avoid dragging her toes.

Case 10

Question 1: What is your differential diagnosis?

- *Is there something wrong with the CNS?*

Question 2: Which tests would you perform first to confirm this diagnosis? What would you do next?

- *CT? MRI?*
  - *Normal.*
- *Something wrong with the peripheral nervous system*:
  - *Consider nerve conduction studies & electromyography*
- *Would you consider a genetic etiology? Why/why not?*
  - *FAMILY HISTORY!*
- Charcot-Marie-Tooth Disease.
- No cure. Physical therapy improves muscle strength & elasticity. Orthopedic surgery & devices correct deformities & improve mobility.

Case 10: MCQ

Which of the following statements about Charcot-Marie-Tooth (CMT) disease is correct?

A. It is an acquired demyelinating polyneuropathy.

B. It primarily affects the central nervous system.

C. It is characterized by progressive distal muscle weakness and sensory loss.

D. It is caused exclusively by autosomal recessive inheritance.

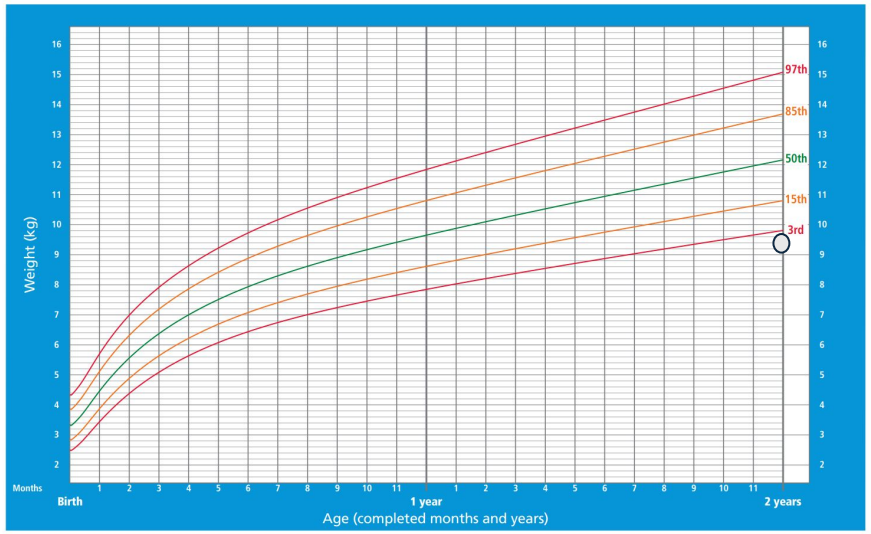
Case 11

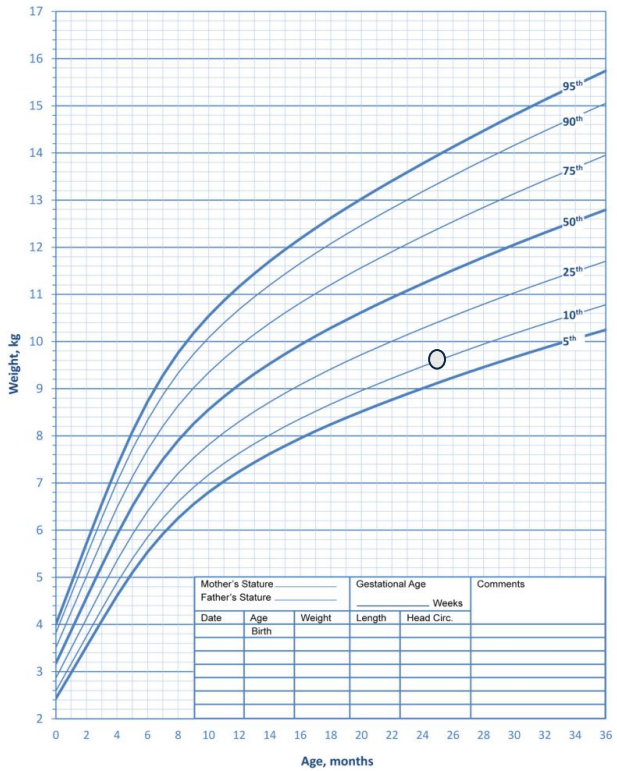
A 24-month-old boy is brought to the pediatric clinic for evaluation of poor growth and frequent respiratory infections. His parents report that he has been hospitalized twice in the past year for pneumonia. They also mention concerns about his delayed speech and difficulty keeping up with peers in motor development. On examination, you note hypotonia and a systolic heart murmur. His weight is 9.5 kg, and his height is 78 cm. A review of his records reveals a history of neonatal jaundice and feeding difficulties as an infant.

Weight-for-age BOYS

Birth to 2 years (percentiles)

World Health Organization

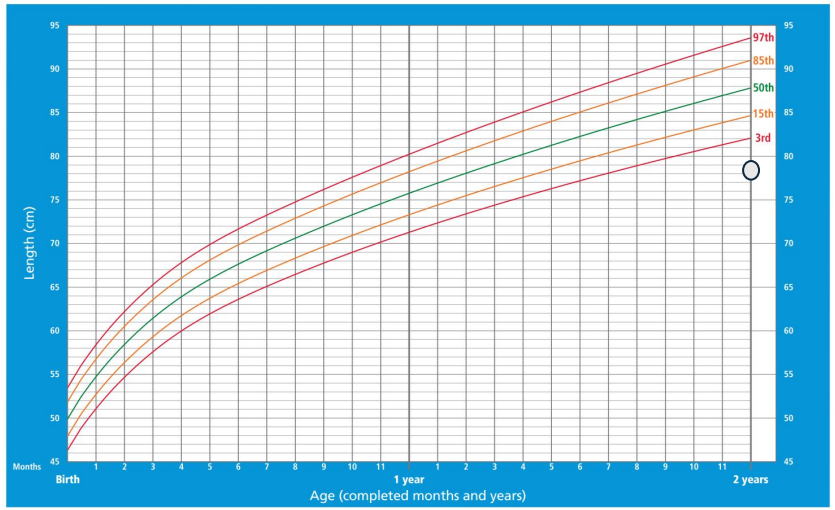


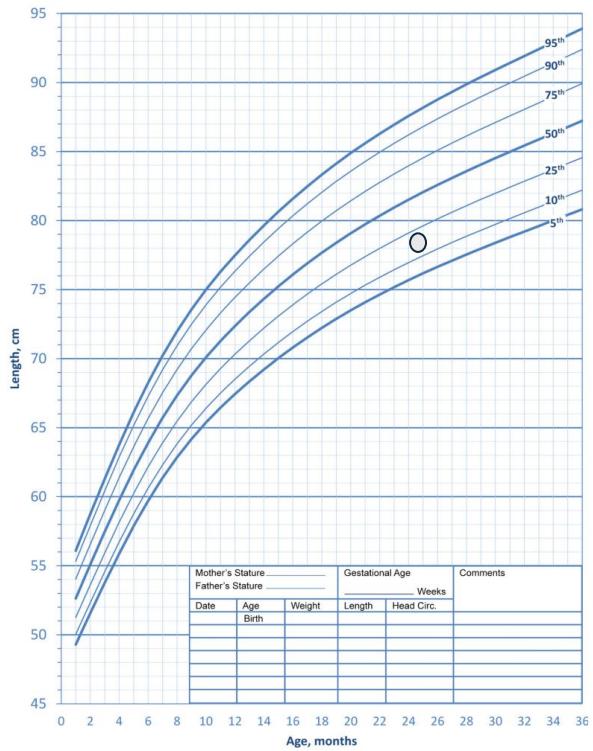


Length-for-age BOYS

Birth to 2 years (percentiles)

World Health Organization





Case 11

Task: Describe the dysmorphism and suggest a diagnosis.

- Flat face
- Epicanthal folds
- Flat nasal bridge
- Upward-slanting palpebral fissures
- Small nose & mouth
- Protuberant tongue
- Low-set and small ears
- Short neck, excessive nuchal skin
- Short extremities
- Big gap between the first toe and others
- Single transverse palmar crease
- Short fifth finger with clinodactyly

Case 11

Question: What congenital and medical conditions are commonly associated with this syndrome, and which ones might explain this child's symptoms? What further evaluations and management strategies would you consider to address this child's current health concerns?

- **Cardiac:** aorto-ventricular septal defect (AVSD)
- **Neurodevelopmental:** developmental delay, intellectual disability
- **Endocrine:** hypothyroidism, obesity
- **GI:** duodenal atresia, celiac disease
- **GU:** cryptorchidism, infertility
- **Hematologic:** anemia, increased risk of leukemia
- **Psychiatric:** early onset dementia, major depressive disorder
- **Neurological:** seizures
- **Other:** cataracts, hearing loss, frequent otitis media

Case 11: MCQ

Which of the following is not a characteristic complication of Down syndrome?

A. Endocrinological: hyperthyroidism and obesity

B. GI: celiac disease

C. Cardiac: AVSD

D. Hematologic: increased risk of leukemia

Case 12

A 1-year-old girl is brought to a pediatric neurologist due to developmental delay in both psychomotor and cognitive domains, along with uncontrolled seizures.

During history-taking, the mother reports that she did not receive prenatal care, delivered the child at home, and has never taken her to a doctor. The child is unvaccinated and did not undergo newborn screening. The mother, who identifies as an expert in natural medicine, states she saw no need for medical evaluation until now.

On physical examination, the child appears malnourished and hypotonic, despite the mother's claim that she feeds her a varied diet without restrictions. During the exam, the child experiences three short tonic seizures, each lasting several seconds. Additionally, a distinct musty odor is noted on her skin and diaper area.

Case 12

Question 1: What is your differential diagnosis? What tests would you perform?

- *Redo newborn screening?*
- *Chromatography / tandem mass spectrometry shows increased phenylalanine concentration.*

Question 2: What treatment recommendations would you give?

- Low phenylalanine diet!

Case 12: MCQ

Which of the following products does not contain phenylalanine?

A. Turkey meat

B. Canned tuna in water

C. Boiled beans

D. All of the above contain phenylalanine

Case 13

A 12-month-old girl presents to the clinical geneticist for a consult. She was born at term, with a birth weight of 4,0kg and a height of 54cm. Her current body weight is 11,5kg, and her height is 81cm. Her mother says that “she has always looked strange.” Upon physical examination you see findings presented in the pictures, a large painless mass in the left lower abdominal quadrant and hypertension.

Orthobullets. (n.d.). *Beckwith-Wiedemann syndrome*. Retrieved January 31, 2025, from https://www.orthobullets.com/pediatrics/4110/beckwith-wiedemann-syndrome

Medizzy. (n.d.). *[Medical image]*. Retrieved January 31, 2025, from https://medizzy.com/feed/30886064

Case 13

Task: Describe the dysmorphism:

- Coarse facial features
- Ear deformity / crumpled ear
- Macroglossia
- Hemihypertrophy

Question 1: What is your differential diagnosis? What tests would you perform (genetic and otherwise).

- Symptoms and MS-MLPA

Question 2: What treatment recommendations would you give? Where would you immediately refer the girl?

- Risk of neoplasia! Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma.
- Heart defects, kidney defects

Orthobullets. (n.d.). *Beckwith-Wiedemann syndrome*. Retrieved January 31, 2025, from https://www.orthobullets.com/pediatrics/4110/beckwith-wiedemann-syndrome

Medizzy. (n.d.). *[Medical image]*. Retrieved January 31, 2025, from https://medizzy.com/feed/30886064

Case 13: MCQ

Beckwith-Wiedemann syndrome is characterized by the presence of:

A. Macrosomia, macroglossia, hemihypertrophy, and a tendency for endocrinopathies during puberty.

B. Macrosomia, macroglossia, hemihypertrophy, and an increased incidence of embryonal tumors in early childhood.

C. Macrosomia, congenital absence of the iris, and the presence of neuroendocrine tumors.

D. Genitourinary and cardiovascular abnormalities, intellectual disability, and an increased incidence of renal sarcomas.

Case 14

A 3-year-old boy is brought to the pediatric clinic due to chronic cough, recurrent respiratory infections, and poor weight gain despite a good appetite. His mother mentions that his stools are bulky, greasy, and have a foul odor. She also notes that he tastes "salty" when she kisses him.

Prenatal history: G1-uncomplicated, natural childbirth, 39Hbd, birth weight 2500g. He passed meconium of a rather hard consistency during the 7th day of life. He presented with prolonged jaundice. His other past medical history includes multiple episodes of pneumonia and prolonged hospitalizations for respiratory distress. Newborn screening results were reportedly abnormal, but follow-up was never completed.

On examination, he appears thin with a weight below the 3rd percentile, has digital clubbing, and has coarse crackles and wheezing on lung auscultation. A chest X-ray shows hyperinflation and bronchiectasis.

Radiopaedia. (n.d.). *Cystic fibrosis (pulmonary manifestations).* Retrieved February 1, 2025, from https://radiopaedia.org/articles/cystic-fibrosis-pulmonary-manifestations-1

Case 14

Question 1: What is your leading diagnosis, and what key pathophysiological mechanism explains these symptoms?

- Cystic fibrosis (CF).
- *CFTR* mutation (Cystic Fibrosis Transmembrane Conductance Regulator), epithelial cell chloride channel.
- The most common mutation is ΔF508.
- Impaired chloride and bicarbonate transport thick, sticky mucus in lungs (chronic infections, bronchiectasis).
- Pancreas: mucus blocks pancreatic ducts, preventing enzyme secretion, causing malabsorption, steatorrhea, and failure to thrive.
- Sweat glands: chloride is not reabsorbed, causing salty sweat.
- GI tract: Meconium ileus in newborns; later, risk of intestinal obstruction.

Case 14

Question 2. What diagnostic tests would you perform to confirm the diagnosis, and what results would you expect?

- Newborn screening.
- Sweat chloride test.
- Genetic testing: CFTR mutation analysis

Case 14

Question 3. What are the key aspects of long-term management for this condition, and how do they address the underlying pathology?

- Respiratory rehabilitation / Airway clearance therapy, mucolytics
- Pancreatic enzyme replacement therapy
- Fat-soluble vitamin supplementation (A, D, E, K).
- High-calorie, high-protein diet.

Case 14: MCQ

Which of the following may occur in a patient with cystic fibrosis?

1) Diabetes
2) Obstruction of the vas deferens
3) Hypertrophic osteoarthropathy
4) Liver cirrhosis
5) Gastroesophageal reflux

The correct answer is:

A. 1,4,5.
B. 1,2,3,4.
C. 1,2,4,5.
D. All of the above.

Case 15

A 5-year-old boy is brought to the dermatology clinic due to concerns about sparse hair, missing teeth, and frequent overheating. His parents report that he barely sweats, even in hot weather, and often becomes flushed and irritable when playing outside. He has had recurrent fevers without clear infectious causes.

On examination, he has thin, lightly pigmented hair and eyebrows, dry skin, and a flattened nasal bridge. His oral exam reveals multiple missing and peg-shaped teeth. His parents state that similar features are present in his older brother, who never underwent any diagnostic processes.

Case 15

Question 1: Based on the clinical presentation and the image provided, what dysmorphic features do you notice, and how might they help narrow the diagnosis?

- Hair is thin and fragile. Thin lips. Thin and fragile nails. Dental pathology.
- They like being in cold places cuz they're always sweating. Why?

Question 2: What is the most likely underlying mode of inheritance of this condition, and how does it explain the patient's symptoms?

- X-linked recessive!

Question 3: What additional evaluations and management strategies should be considered for this child's long-term care?

- Immunodeficiency

Case 15: MCQ

Which of the following is a characteristic feature of ectodermal dysplasia?

A. Hyperhidrosis
B. Polydactyly
C. Hypodontia
D. Increased scalp hair density

Case 16

An 18-year-old male was referred to the genetics outpatient clinic by his endocrinologist. He has a history of learning disabilities at school as well as characteristics of delayed puberty (no voice deepening, no facial hair growth). Physical examination reveals the abnormalities presented in the photo, most notably a slender build with a female-type fatty tissue distribution, prominent ears, a high-pitched voice, genu valgum and small, hard testicles. He has very discrete signs of pubertal development. Family history is unremarkable.

Case 16

Question 1: What is your differential diagnosis?

- Klinefelter Syndrome.
- *Alt: Marfan? Ehlers-Danlos?*

Question 2: What genetic test would you order to confirm this diagnosis? What result would you expect?

- Karyotyping!
- 47,XXY

Question 3: What are the long-term health implications for a patient with this condition?

- Infertility
- Intellectual disability
- Autoimmune disorders
- Breast cancer (why?)
- Venous thromboembolic disease (why?)
- Osteoporosis (why?)

Case 16: MCQ

The main symptom of Klinefelter syndrome in 14–15-year-old boys is:

A. Eunuchoid body habitus.
B. Tall stature
C. Microorchidism
D. Gynecomastia.

Case 17

A 3-year-old boy is brought to the pediatric clinic due to developmental delay, particularly pertaining to language and social skills. His mother reports that he began speaking at 2 years of age but has limited vocabulary and struggles with social interaction. He often avoids eye contact and does not engage in reciprocal conversation. His history is significant for developmental milestones being significantly delayed.

Physical exam reveals findings shown in the picture as well as joint hyperlaxity, echolalia and speech impediment, signs of moderate intellectual disability and signs of behavioral abnormalities (hand-flapping and repetitive behaviors).. The mother mentions that a male cousin had similar developmental issues and was diagnosed with autism spectrum disorder.

Case 17

Task: Describe the patient's dysmorphic features.
Question 1: What is your differential diagnosis? What diagnostic test would you order to confirm the diagnosis?

- Triangle face
- Large protruding ears
- Microcephaly? normocephaly or macrocephaly?
- Large testicles (unseen)
- Severe developmental delay
- *Fragile X syndrome*
- Genetic testing FMR1 / AGG trinucleotide genotyping

Case 17: MCQ

Which of the following statements about Fragile X Syndrome is false:

A. It occurs in boys with a frequency of 1:1250-1500.
B. It is the most common cause of intellectual disability in boys after Down syndrome.
C. The mutation is lethal for girls.
D. Testicular enlargement after puberty is a characteristic symptom.

Case 18

A 13-year-old boy is brought to the genetics outpatient clinic due to concerns about developmental delay, difficulty feeding, and abnormal behaviors. His mother reports that he has had a history of poor feeding and failure to thrive during infancy, but his appetite has increased significantly during puberty. The boy demonstrates severe developmental delay. He is unable to walk independently and has a limited vocabulary. He has episodes of inappropriate laughter bursts. Upon physical examination global hypotonia, short stature, and obesity were noted.

Case 18

Question 1: Pretend the patient in the left picture is described. What is your differential diagnosis? Why? Briefly describe the dysmorphism.

- Obesity (not dysmorphism…)
- Hypomimia/ generalized hypotonia
- Open mouth – dry saliva
- *Prader-Willi Syndrome*

Case 18

Question 2: Pretend the patient in the right picture is described. What is your differential diagnosis? Why? Briefly describe the dysmorphism.

- Prominent nasal bridge
- Large lower jaw, open mouth.
- Prominent dimples – facial hypotonia
- *Angelman syndrome* –
    - behavioral phenotype, no consistent dysmorphism.

Case 18

Question 3: What is the genetic mechanism that differentiates Prader-Willi from Angelman syndrome, and how do these mechanisms explain the observed symptoms in this child?

- Imprinting! Methylation to “turn off” genes.
- Maternal vs. Paternal inheritance.

Case 18: MCQ

Growth Hormone supplementation therapy can be used routinely to treat children with:

A. Prader-Willi Syndrome

B. Angelman Syndrome

C. Both A and B

D. Neither A nor B

Case 19

A 3-year-old boy is brought to the pediatric clinic for a routine check-up. He is noticeably shorter than other children his age and his legs appear bowed when he walks. He began walking at around 18 months and tends to waddle. Despite his short stature, his motor and cognitive development appear appropriate for his age. Family history is unremarkable.

On physical examination, his height is significantly below the standard growth chart for age, but he follows a typical growth curve.

Case 19

Question 1: Describe the dysmorphism and suggest a diagnosis.

- Disproportionate short stature (how do you know?)
- Genu varum, short bones
- Flat face, nasal anomaly
- Protruding forehead
- Trident hand (not shown)
- *Achondroplasia*

Case 19

Question 2: What are the most important complications associated with this condition, and how should they be monitored or managed?

- Chronic pain, recurrent AOM, complications of short stature

Question 3: What would you tell the parents regarding inheritance risk, especially considering that neither parent has the condition?

- De novo?

Case 19: MCQ

A couple with autosomal dominant achondroplasia wishes to have a child. Neither parent has a family history of achondroplasia. The estimated chance of them having a healthy child is:

	A	**a**
A	AA	Aa
a	Aa	aa

A. 75%

B. 50%

C. 25%

D. Equivalent to the general population's risk

Case 20

A 2-year-old boy is brought to the genetics outpatient clinic due to concerns about rapid head growth and developmental delay. His parents report that his head circumference has been consistently above the 98th percentile since infancy. He was born at 41 weeks of gestation, weighing 4.2 kg and measuring 56 cm in length. His motor milestones were slightly delayed—he sat independently at 9 months and walked at 18 months. His speech is also delayed. There is a history of recurrent otitis media, and his mother mentions that he is socially anxious and avoids eye contact. His fontanelles closed around the age of 6 months. The parents are healthy, family history is unremarkable.

Case 20

Task: Describe the dysmorphism seen upon physical examination.

Question 1: What is the most likely diagnosis?

- Wide forehead.
- Narrow temples
- Macrocephaly – “overturned pear”
- Developmental delay
- Short nose
- *Sotos Syndrome / Craniosynostosis family*

Question 2: What are the key medical concerns associated with this condition, and how should the patient be monitored over time?

- Neurosurgical intervention!

Case 20

Describe the dysmorphism. Who's affected? Why?

- Father's affected for sure.
- Flat occiput.
- Abnormal head shape
- Premature fontanelle closure. Wide forehead.
- Craniosynostosis. What are we afraid of? Craniostenosis.
- How about the child?
- *Cruzon syndrome*