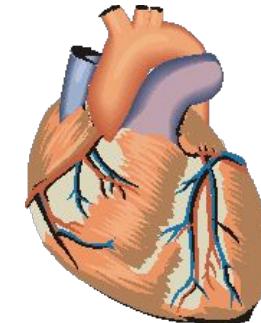


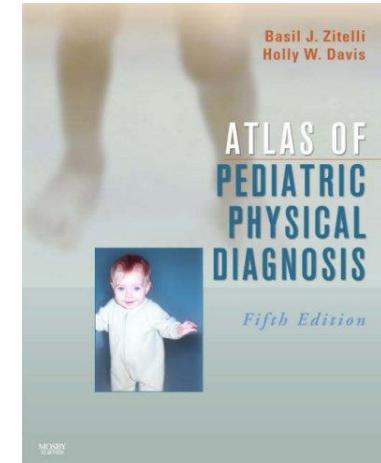
Genetic syndromes Involving the Heart

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Goals and Objectives

- To review common genetic syndromes associated with CHD in an interactive case-based format
 - Focus on high-yield images



Exam Weights

The tables below indicate exam weights (ie, the percentage of test questions that fall within each content domain and each universal task) for all three General Pediatrics examinations (initial certification, maintenance of certification, and in-training).

Content Domain	Exam Weight
1. Preventive Pediatrics/Well-Child Care	8%
2. Fetal and Neonatal Care	5%
3. Adolescent Care	5%
4. Genetics, Dysmorphology, and Metabolic Disorders	3%
5. Mental and Behavioral Health	5%
6. Child Abuse and Neglect	4%
7. Emergency and Critical Care	4%
8. Infectious Diseases	7%
9. Oncology	2%
10. Hematology	4%
11. Allergy and Immunology	4%
12. Endocrinology	4%
13. Orthopedics and Sports Medicine	4%
14. Rheumatology	2%
15. Neurology	5%
16. Eye, Ear, Nose, and Throat	4%
17. Cardiology	4%
18. Pulmonology	5%
19. Gastroenterology	4%
20. Nephrology, Fluids, and Electrolytes	4%
21. Urology and Genital Disorders	3%
22. Skin/Dermatology	4%
23. Psychosocial Issues	2%
24. Ethics	2%
25. Research Methods, Patient Safety, and Quality Improvement	2%
Total	100%

Universal Task	Exam Weight
1. Basic Science and Pathophysiology	20%
2. Epidemiology and Risk Assessment	10%
3. Diagnosis	35%
4. Management and Treatment	35%
Total	100%

Case #1

- Ten year-old girl presents for WCC
- PE: Missing thumbs on both hands
- CV: Widely split fixed S₂, a 2/6 SEM at the ULSB, and a 1/6 short mid-diastolic murmur at the LLSB



Case #1

- FHx – Different members of the family with heart murmurs, radial anomalies, and cardiac conduction defects

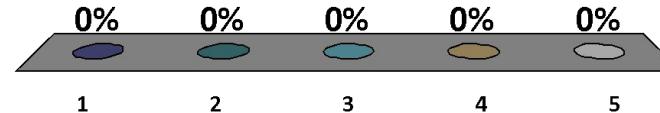


What is the most likely cardiac defect?

- 0% (A) ASD
- 0% (B) VSD
- 0% (C) PDA
- 0% (D) Tetralogy of Fallot
- 0% (E) Dextrocardia, TGA, and IAA

Which of the following is the most likely genetic syndrome?

- (A) VACTERL
- (B) Holt-Oram
- (C) Pulmonary Atresia with multiple collaterals
- (D) Kabuki
- (E) M...



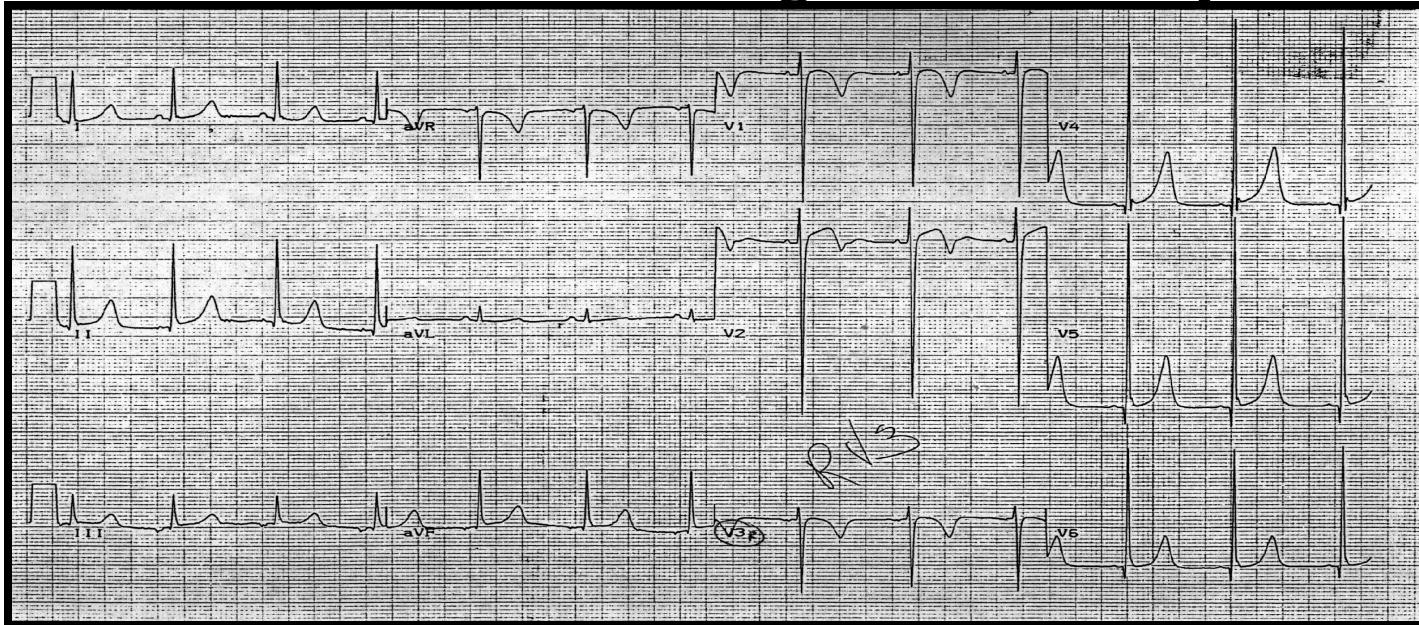
Holt-Oram

- Typically Autosomal Dominant
 - **TBX5 gene mutation**
 - Preaxial radial ray abnormalities of upper limbs
- Severe (phocomelia) or more mild (hypoplasia) of involved bones
- Cardiac conduction defects can be present

Case #2

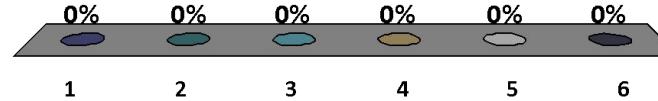
- ♥ Hx – 1 year-old boy with mild mental retardation and 2 day Hx of URI symptoms
- ♥ PE - 5/6 SEM URSB
- ♥ BP 107/60 mm Hg
- ♥ Calcium is 12mg/dL

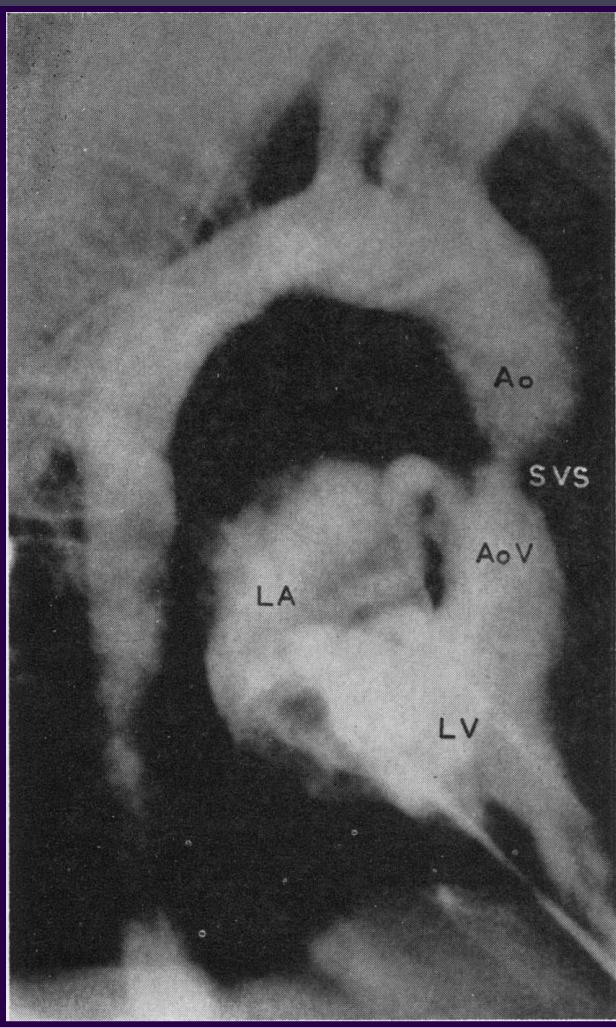
- EKG reveals the following abnormality



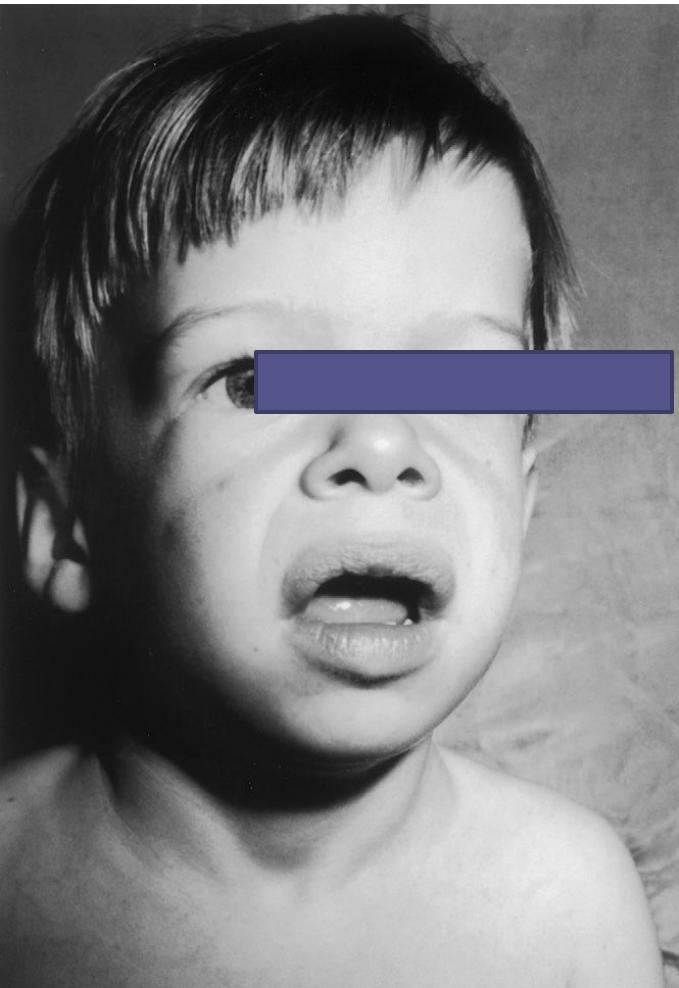
What is the most likely cardiac diagnosis?

- (A) ASD
- (B) VSD
- (C) PDA
- (D) PS
- (E) AS
- (F) Innocent murmur





- Williams, JCP, Barratt, BG, et al.. SAS. *Circulation*. 1961;24:1311-1318

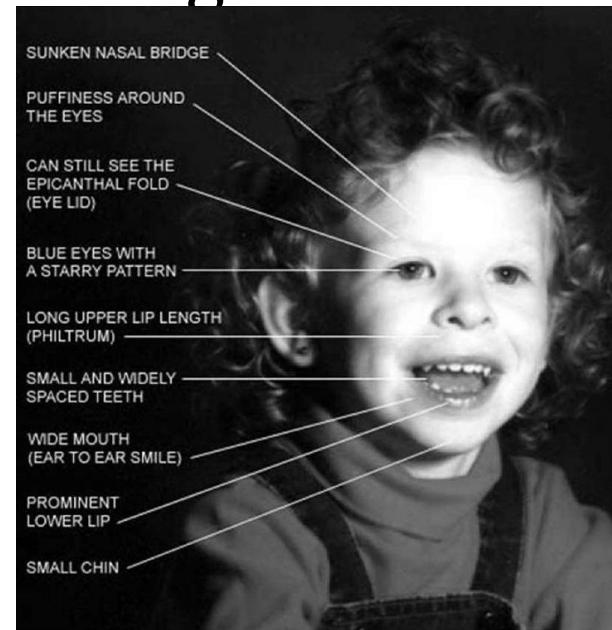


Your diagnosis?

- 0% • (A) Williams syndrome
- 0% • (B) Kabuki syndrome
- 0% • (C) Alagille syndrome
- 0% • (D) Wolf-Hirschhorn Syndrome
- (E) Trisomy 21

Williams Syndrome

- Elastin gene disruption involving chromosome 7



- Stellate iris
- Short nose with bulbous nasal tip
- Flat nasal bridge
- Prominent full cheeks
- Long philtrum
- Wide mouth



Williams Syndrome

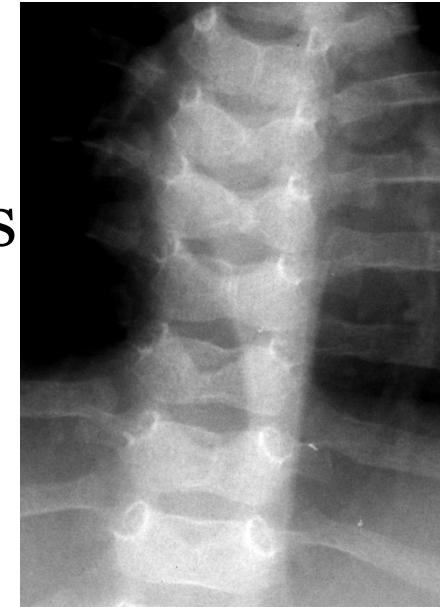
- Cardiac manifestations include
 - Supravalvar aortic stenosis
 - Supravalvar pulmonary stenosis
 - Peripheral branch pulmonary artery stenosis
 - Renal artery stenosis
 - Systemic hypertension

Williams Syndrome

- Variable mental retardation
- Delayed speech acquisition, followed by excessive talking, and overfriendly behavior (“cocktail party” persona), hyperacusis
- Behavioral problems –ADHD, Anxiety
- Hypercalcemia

Case #3

- ♥ 7 year-old girl with a systolic murmur at the left and right axilla and back
- ♥ Hypercholesterolemia
- ♥ Butterfly-like vertebral arch defects
- ♥ Mild mental retardation
- ♥ Growth restriction

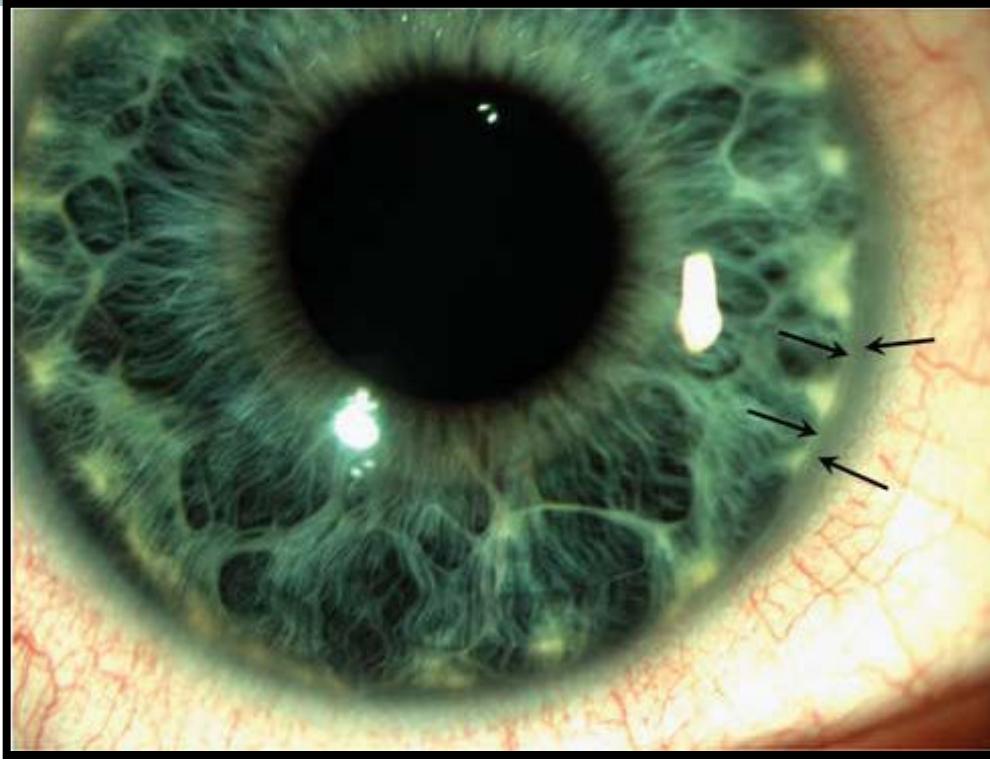






- Broad prominent forehead
- Deep-set, widely spaced eyes
- Long straight nose
- Underdeveloped mandible





- Posterior embryotoxin at the junction of the iris and cornea

Liver biopsy

- Paucity of interlobular bile ducts
- Cholestasis in hepatocytes and canaliculi



Which of the following is the most likely genetic syndrome?

- 0% (A) Noonan's syndrome
- 0% (B) Cri-du-chat
- 0% (C) Angelman Syndrome
- 0% (D) Alagille Syndrome
- 0% (E) Apert Syndrome

Alagille Syndrome

- Most patients present with neonatal jaundice
- Cholestasis develops in patients up to 3 years
- AD - JAG1(90%)

Case #4

- 3 y/o with seizures, hypopigmented macules and developmental delay
- Prenatal echocardiogram demonstrates tumors





What is the usual course of these cardiac masses?

- 0% (A) Progress in size
- 0% (B) Regress in size
- 0% (C) Result in obstruction in cardiac output
- 0% (D) Require surgical excision

Which of the following is the most likely genetic diagnosis?

- 0% (A) Waardenburg syndrome
- 0% (B) Treacher Collins
- 0% (C) Sturge Webber
- 0% (D) Smith-Lemli-Opitz
- 0% (E) Tuberous Sclerosis

Tuberous Sclerosis

- AD – TSC2 (~70%), TSC1 (~26%)

Adenoma Sebaceum



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White ash-leaf spots

- Present in 90% of cases, common on trunk and buttocks



Shagreen Patch

- A form of collagenoma
- Elevated discolored skin commonly observed over lumbosacral region (> 90%)



Facial Angiofibroma

- Red/Brown nodules over nose and cheeks





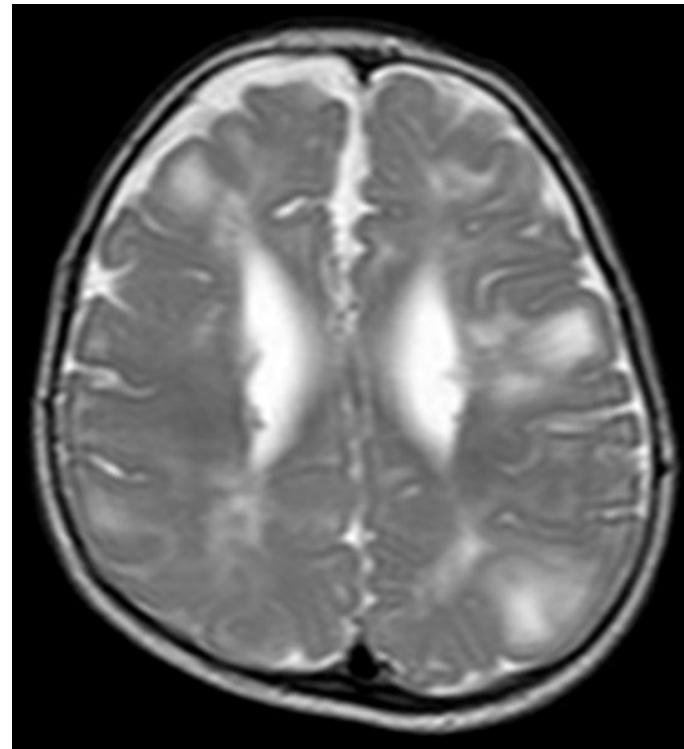
- Forehead fibrous plaque – yellowish-brown or skin-colored plaque



- Periungual fibroma

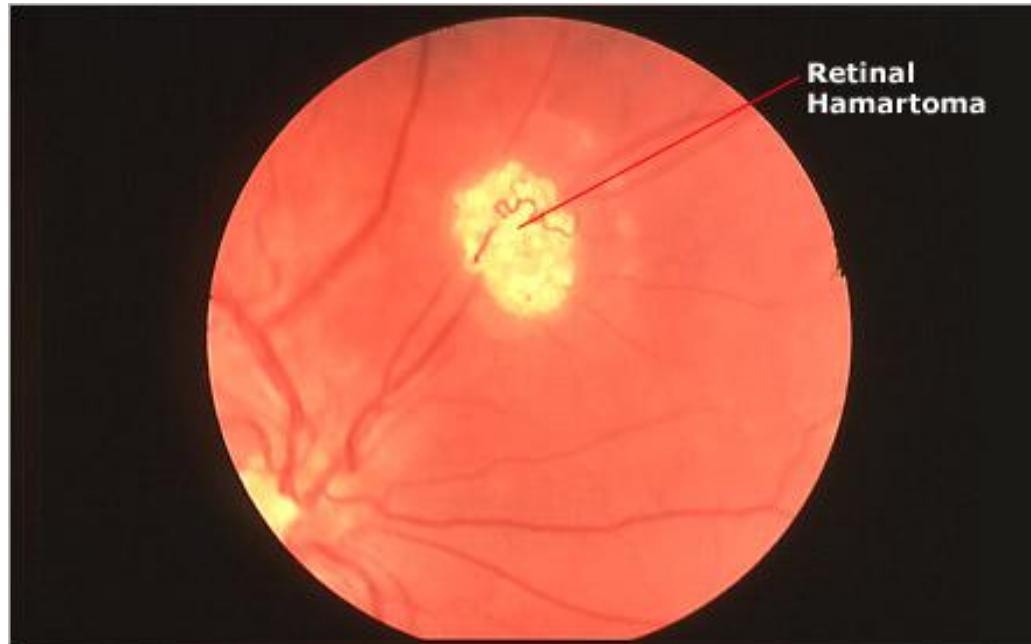
CNS Abnormalities

- Subependymal nodules (~80%)
- Cortical dysplasias
- Subependymal giant cell astrocytomas
- 80% have seizures
- Autism (20-60%)



Retinal Hamartoma

- 30-50%

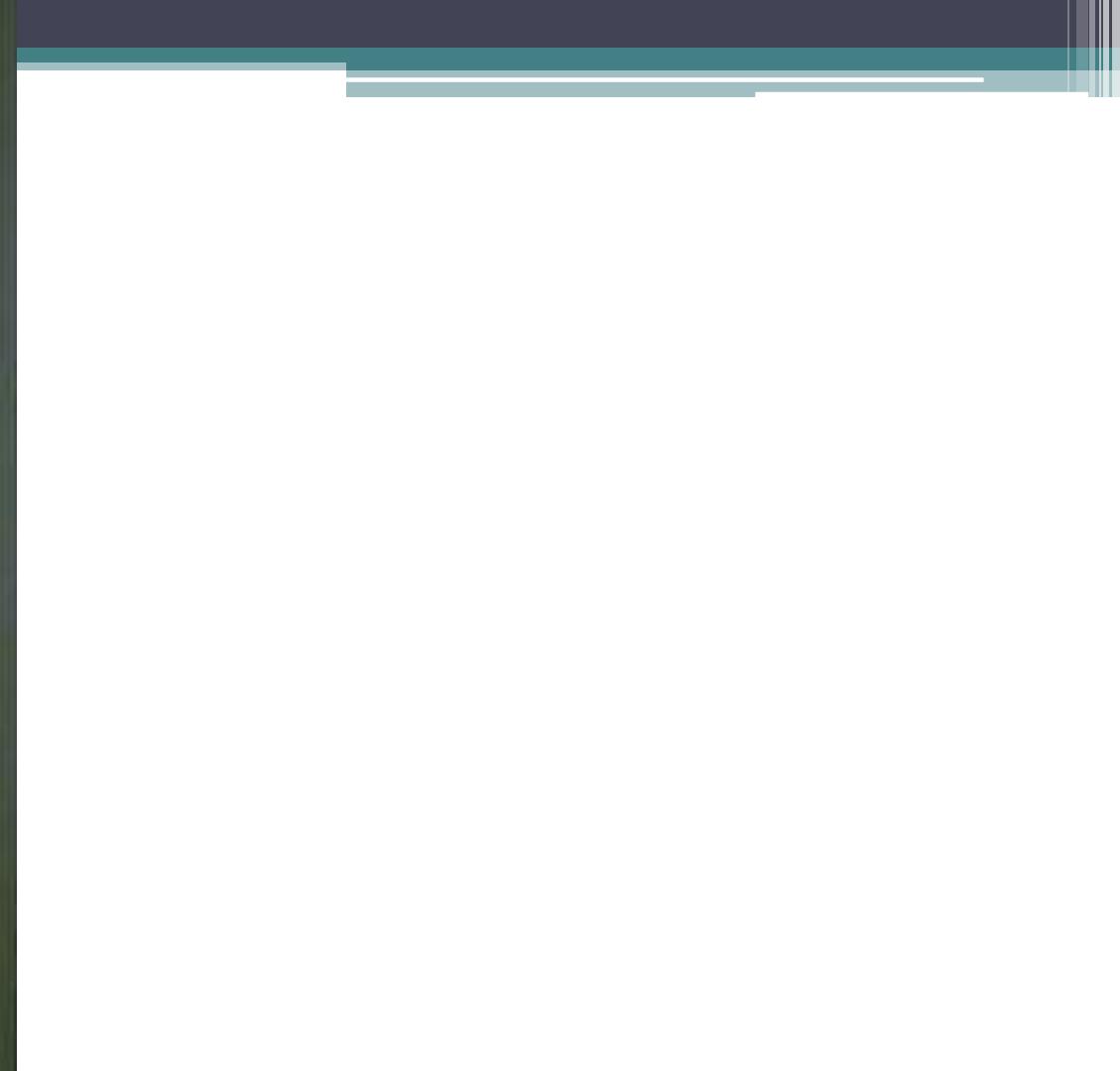


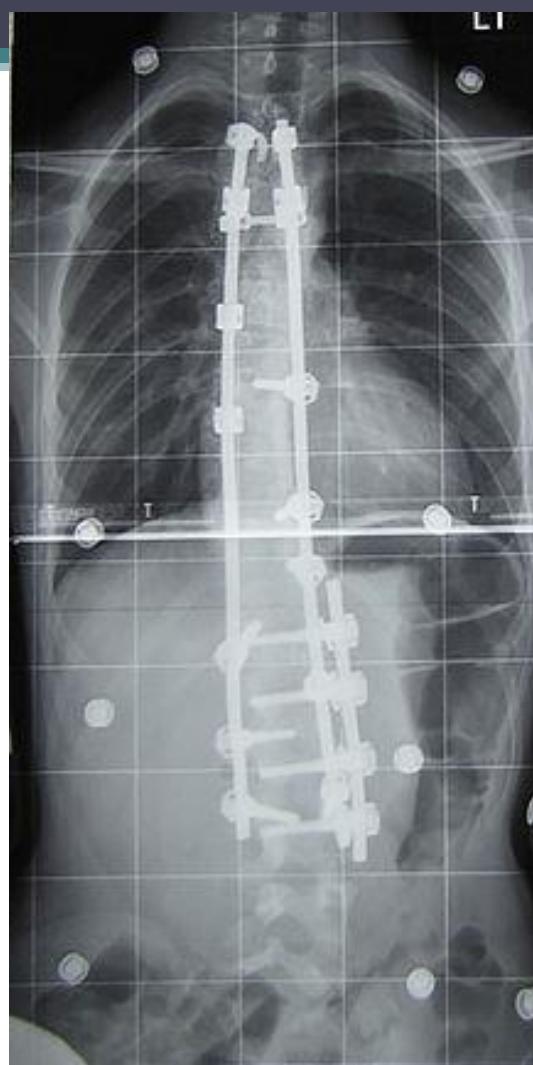
Case #5

- ♥ 18 year-old male with pectus carinatum, flat feet, and pneumothorax
- ♥ CV: Mid-systolic click, followed by a 3/6 apical systolic murmur.
- ♥ History of lens subluxation.

What is the most likely congenital heart defect?

- 0% (A) Aortic stenosis
- 0% (B) Pulmonary stenosis
- 0% (C) Coarctation of the Aorta
- 0% (D) Pericarditis
- 0% (E) Mitral valve prolapse with regurgitation



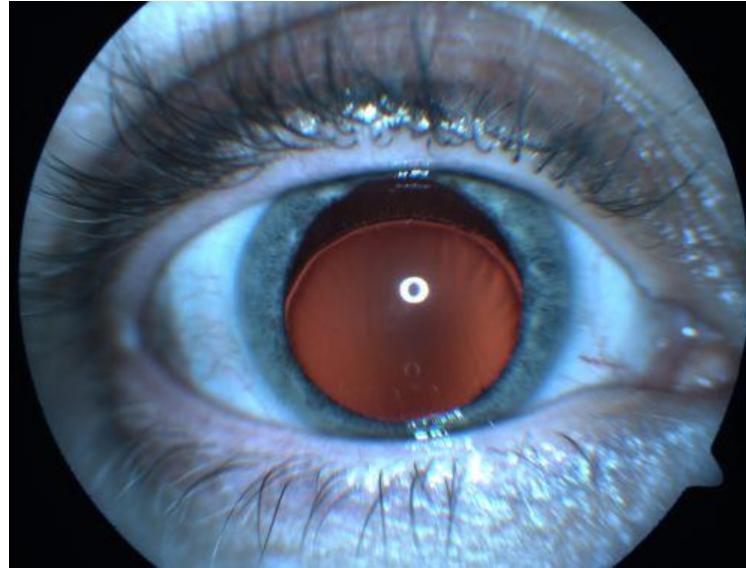




- Reduced extension of the elbows ($<170^\circ$)



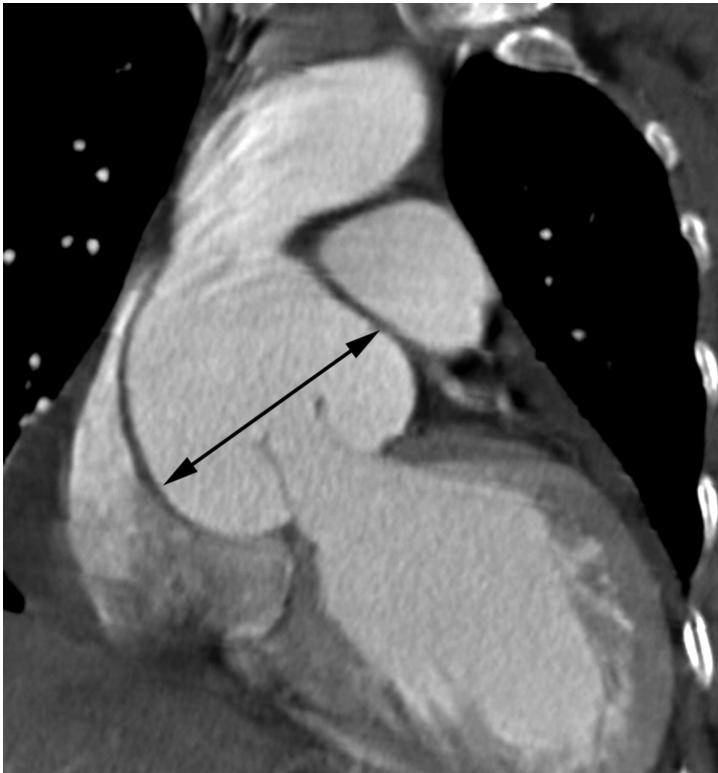
- Medial displacement of the medial malleolus, causing pes planus



- Ectopia Lentis

Which of the following is the best diagnosis?

- 0% • (A) Marfan syndrome
- 0% • (B) Treacher Collins
- 0% • (C) Sturge Webber
- 0% • (D) Smith-Lemli-Opitz
- (E) Neurofibromatosis



Ha H I et al. Radiographics 2007;27:989-1004

RadioGraphics

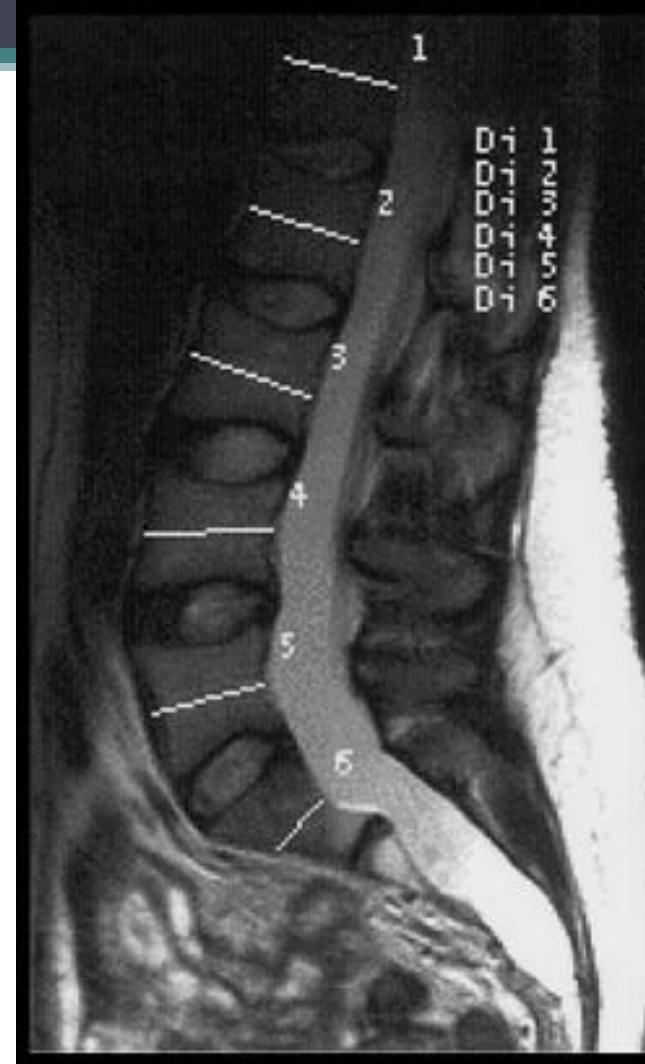


39.4mm/rot
0.6sp

Volume Rendering

DFC

- Lumbosacral dural ectasia
 - (stretching of dural sac)



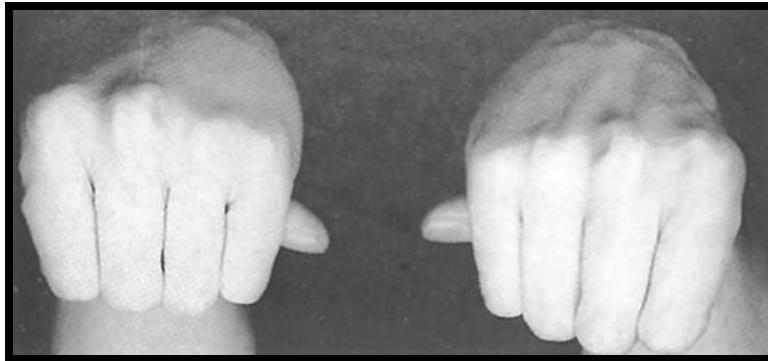


Table 1 | Diagnostic criteria for Marfan syndrome*²

Organ system	Requirement for classification of organ system as meeting a major criterion	Requirement for classification of organ system as being 'involved'
Skeletal system	At least four of the following features: 1. Pectus carinatum 2. Pectus excavatum requiring surgery 3. Reduced upper to lower segment ratio or increased arm-span to height ratio (>1.05) 4. Positive wrist and thumb signs 5. Scoliosis (>20°) or spondylolisthesis 6. Reduced extension of the elbows (<170°) 7. Medial displacement of the medial malleolus causing pes planus 8. Protrusio acetabulae of any degree	At least two features contributing to major criterion, or one feature from that list and two of the following minor criteria: 1. Pectus excavatum of moderate severity 2. Joint hypermobility 3. Highly arched palate with dental crowding 4. Characteristic facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Ocular system	Ectopia lentis	At least two of the following minor criteria: 1. Abnormally flat cornea 2. Increased axial length of globe 3. Hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis
Cardiovascular system	At least one of the following features: 1. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva 2. Dissection of the ascending aorta	At least one of the following minor criteria: 1. Mitral valve prolapse with or without regurgitation 2. Dilatation of the pulmonary artery, in the absence of valvular or peripheral stenosis or any other obvious cause, in individuals younger than 40 years of age 3. Calcification of the mitral annulus in individuals younger than 40 years of age 4. Dilatation or dissection of the descending thoracic or abdominal aorta annulus in individuals younger than 50 years of age
Pulmonary system	None	At least one of the following minor criteria: 1. Spontaneous pneumothorax 2. Apical blebs
Integumentary system	None	At least one of the following minor criteria: 1. Stretch marks not associated with marked weight changes, pregnancy or repetitive stress 2. Recurrent or incisional herniae
Dura	Lumbosacral dural ectasia by CT or MRI	None

*For a diagnosis of Marfan syndrome in patients with no family background of this disease, two different organ systems must be classified as meeting the major criteria and there should be data suggesting at least the 'involvement' of a third system. In patients with a family history of Marfan syndrome, only one major criterion need be met, along with data suggesting the involvement of a second system.

What if your “Marfan syndrome” patient had....



Cleft palate

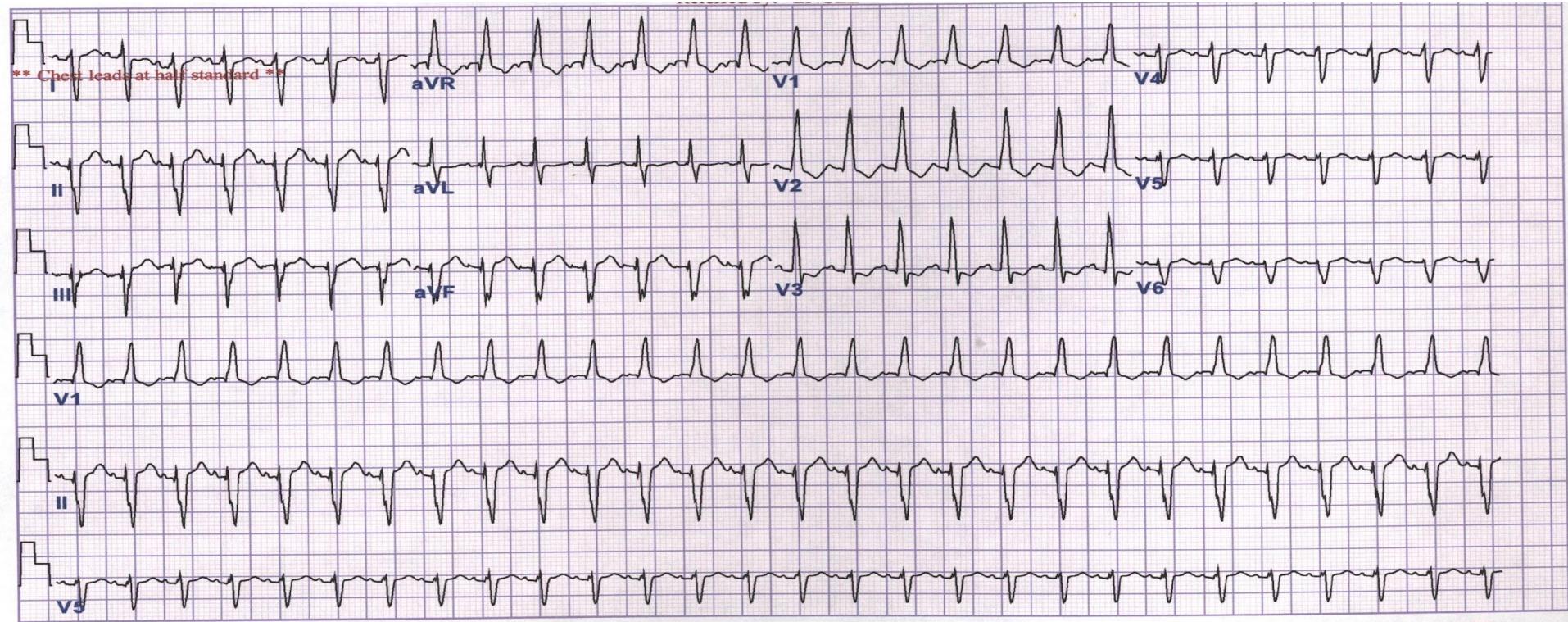


Loeys-Dietz syndrome

Case #6

- ♥ 4 month old “dysmorphic boy” presents for WCC
- ♥ Patient is undernourished, tachycardic and tachypneic.
- ♥ 3/6 holosystolic murmur along LLSB, and mid-diastolic rumble.
- ♥ Hepatomegaly

EKG demonstrates this abnormality



Which of the following is the best diagnosis?

- 0% (A) McCune-Albright
- 0% (B) Treacher Collins
- 0% (C) Sturge Webber
- 0% (D) Trisomy 21
- 0% (E) Neurofibromatosis

Your Diagnosis

- ♥ Trisomy 21



Trisomy 21

- Typical physical phenotype due to an extra copy of the proximal part of 21q22
- Types of Trisomy 21
 - 94% Full trisomy 21
 - 2.4% Mosaicism
 - 3.3% Translocation

- Short stature
- Hypotonia
- Moderate-to-severe mental retardation
- Sleep apnea

- Brushfield spots
- Refractive errors (50%)
- Strabismus (44%)
- Nystagmus (20%)



- Upslanting palpebral fissures
- Flat nasal bridge
- Partial adontia or microdontia (50%)



Trisomy 21

- Ears – small, over-folded helix
- Hearing loss is common
- Neck – Atlantoaxial instability

Trisomy 21

- 40-50% of patients will have congenital heart disease
- 43% AV canal
- 32% VSD

Karthik, av canal
00-06-09-124208

GOVT GEN HOSPITAL, CHENNAI.

6/9/2000 PHILIPS
12:11:50 PM

5 HD

L.H.
SI-2
MI 1.6
TTS 1.0
H3 Ein 38
232dB/C3
D/2/0

200Hz 12cm

1.0 3.8

Trisomy 21

- GI/Abdomen
- Diastasis recti
- Umbilical hernia
- Duodenal atresia
- Hirschprung disease
- TE fistula

single palmer
crease, short
fifth finger that
curves inward



widely separated
first and second
toes and increased
skin creases



Trisomy 21

- Endocrine
 - Hypothyroid
 - Diabetes
- Hematologic
 - Neonatal leukemoid reaction
 - Increased risk of leukemia

Case #7

- ♥ Female infant with a single umbilical artery.
- ♥ Profound psychomotor delay, mental retardation, hypotonia, and seizures
- ♥ Low birth weight, microcephaly, micrognathia, ed fists with overlapping fingers.



Case #7

- There is microcephaly, cerebellar hypoplasia, microphthalmia, low set, malformed ears, and a short sternum
- 3/6 holosystolic murmur LLSB



What is the likelihood of congenital heart disease in this child?

- 0% (A) under 5%
- 0% (B) 10%
- 0% (C) 20%
- 0% (D) 50%
- 0% (E) Over 90%

What is the most likely genetic condition?

- 0% (A) Trisomy 18
- 0% (B) Trisomy 13
- 0% (C) Wolf-Hirschhorn Syndrome
- 0% (D) Rett syndrome
- 0% (E) Prader Willi

Trisomy 18

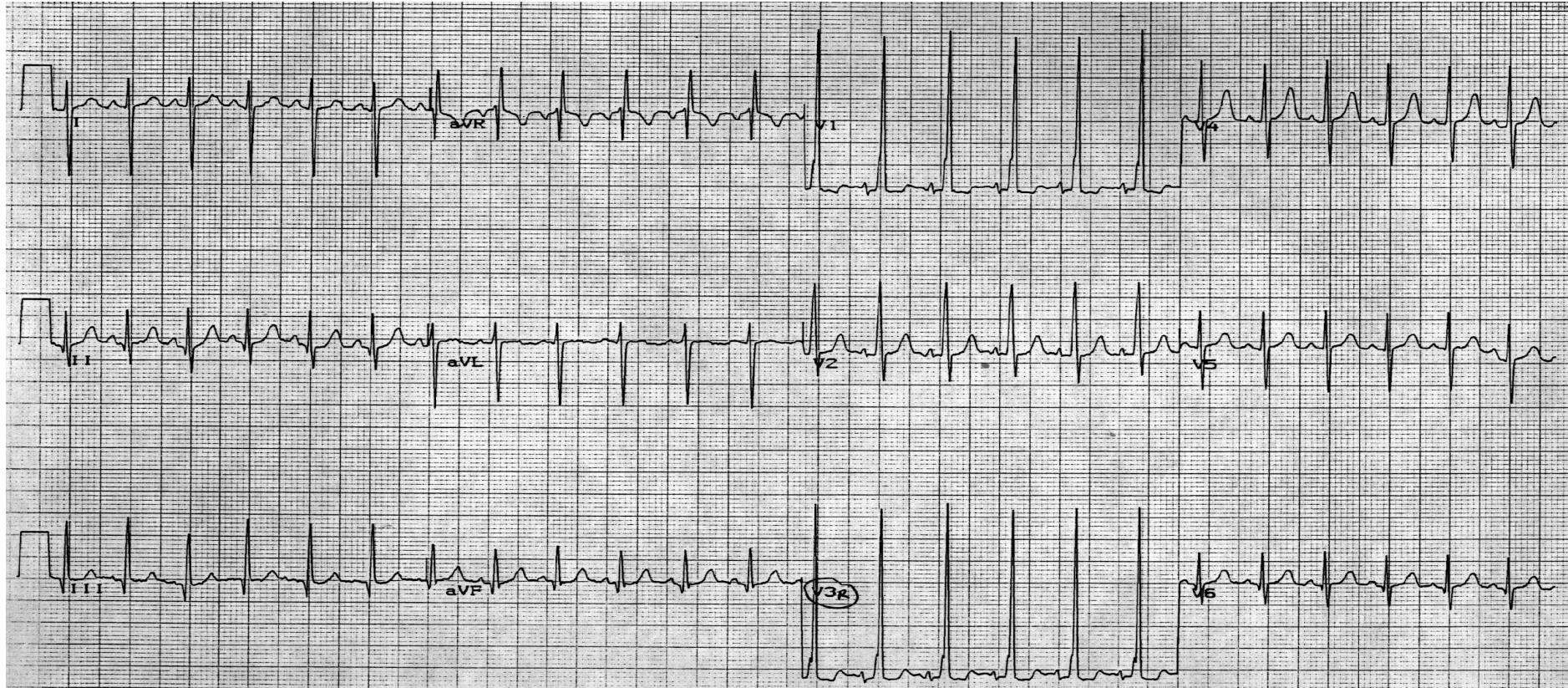
- Additional malformations include
 - Pulmonary hypoplasia
 - GI abnormalities
 - GU abnormalities
 - Endocrine
 - Thymic, thyroid, and adrenal hypoplasia

Trisomy 18

- Most common cardiac problems
 - VSD, ASD, PDA, TOF, coarctation of aorta, bicuspid aortic or pulmonary valve

Case #8

- ♥ 6 year-old short boy, WCC
- ♥ CV: Early systolic click at USB, followed by a 3/6 SEM at LUSB.



Which of the following is the most likely cardiac defect?

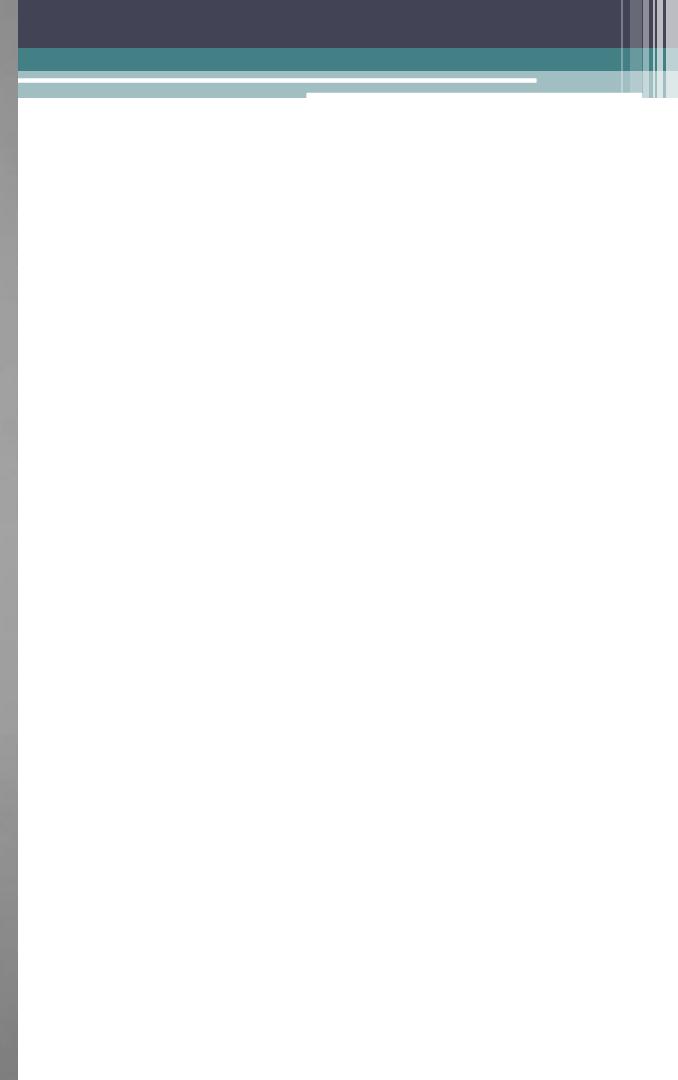
0% (A) Aortic stenosis

0% (B) VSD

0% (C) ASD

0% (D) Pulmonary stenosis

(E) PDA





Short stature

- Up to 83% of patients have short stature¹

Characteristic facial features³

- Broad, high forehead
- Hypertelorism
- Low-set, posteriorly rotated ears with a thick helix
- High-arched palate
- Micrognathia
- High-arched eyebrows¹
- Short neck with excess nuchal skin
- Epicanthal folds
- Downward-slanting palpebral fissures
- Low posterior hairline

Congenital heart defects³

- Pulmonary valve stenosis
- Hypertrophic obstructive cardiomyopathy
- Atrial and ventricular septal defects
- Persistent ductus arteriosus

Other clinical manifestations³⁻⁵

- Pectus carinatum, pectus excavatum
- Scoliosis
- Cryptorchidism
- Lymphatic abnormalities
- Coagulopathy
- Cognitive/learning disabilities
- Ophthalmological issues
- Arnold-Chiari malformation
- Seizures

Which of the following is the most likely diagnosis?

- 0% (A) Leopard syndrome
- 0% (B) Noonan syndrome
- 0% (C) Klippel-Feil syndrome
- 0% (D) Lesch-Nyhan syndrome
- 0% (E) Menkes disease

Genetics in Noonan Syndrome

- Mutation in *PTPN11* (50%), *SOS1* (13%)

Genetic defects

- Pulmonary stenosis (20-50%)
- HCM (20-30%)
- EKG abnormalities (90%)
 - Axis deviation most common

Neonatal features

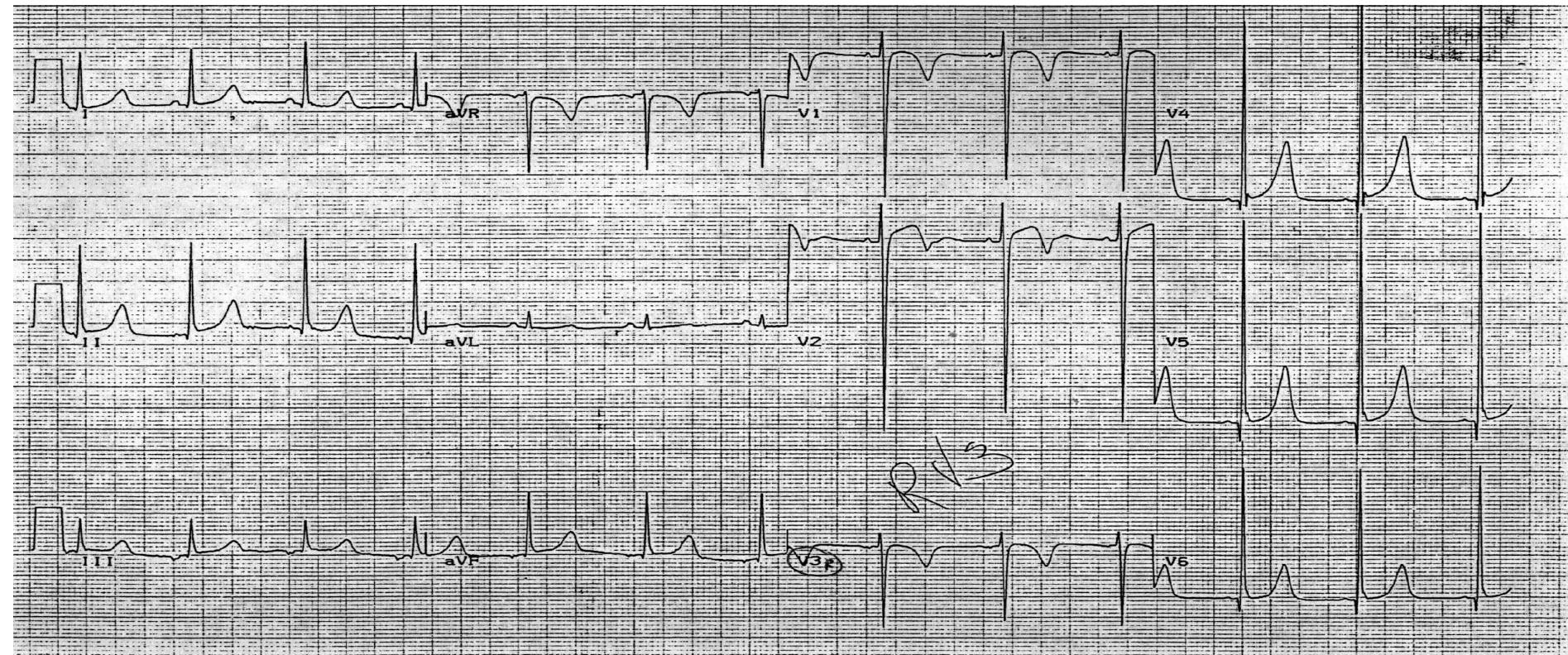
- Tall forehead
- Hypertelorism
- Downslanting palpebral fissures

Posterior view
rotated ears



Case #9

- ♥ 12 year-old short female WCC
- ♥ PE:
 - ♥ Apical ejection click,
 - ♥ 2/6 SEM base that radiates to the carotids



Which of the following is the most likely cardiac defect?

0% (A) Aortic stenosis

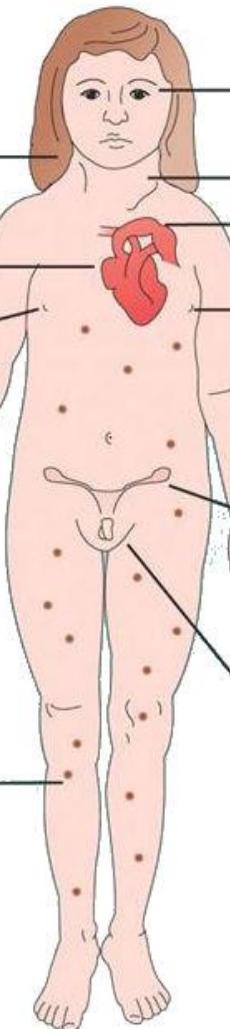
0% (B) VSD

0% (C) ASD

0% (D) Pulmonary stenosis

(E) PDA

Short stature



Characteristic
facial features

Fold of skin

Constriction
of aorta

Poor breast
development

Elbow
deformity

Rudimentary
ovaries
Gonadal streak
(underdeveloped
gonadal
structures)

No menstruation

Low hairline

Shield-shaped
thorax

Widely spaced
nipples

Shortened
metacarpal IV

Small
fingernails

Brown spots (nevi)

What is the most likely genetic defect?

- 0% (A) Turner syndrome
- 0% (B) VATER
- 0% (C) Treacher-Collins
- 0% (D) Stickler syndrome
- 0% (E) Sotos syndrome

Your Diagnosis

- ♥ Turner Syndrome

Turner syndrome

- Caused by a complete or partial X chromosome monosomy.
- Risk of developing gonadoblastoma

Turner syndrome

- Congenital heart defects (30%)
 - Coarctation of the aorta
 - Bicuspid aortic valve
 - Aortic stenosis
 - Aortic root dilation (aneurysm)

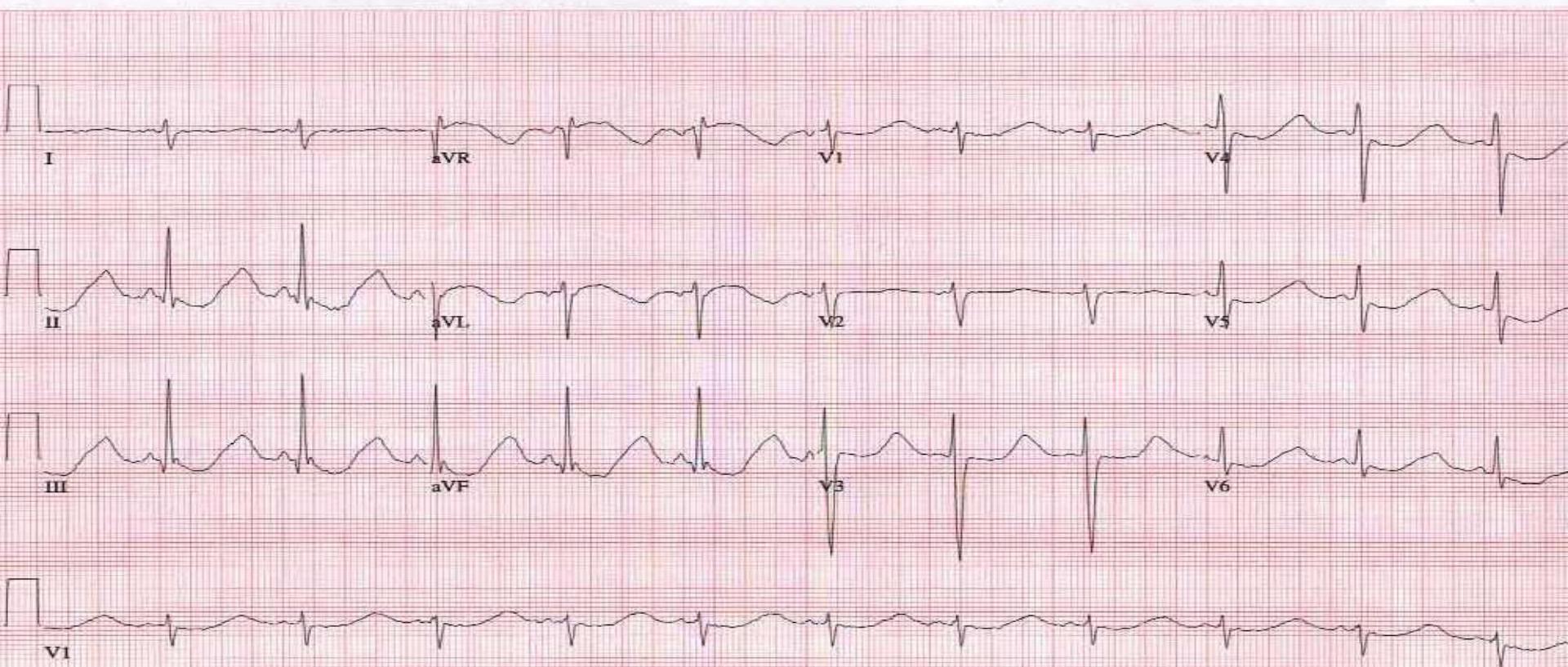
Case #10

- ♥ 12 year old boy with a history of syncope.
- ♥ Family history is significant for a father who drowned unexpectedly while at swimming. He was a member of the varsity swim team.
- ♥ Paternal uncle has a history of syncope.
- ♥ Paternal grandfather with a history of sudden death from unknown causes at 22 years of age.

20 yr
Female Caucasian

Room:ICU S
Loc:2

Technician: 02



Which of the following is the most likely diagnosis?

0%

(A) Hypertrophic cardiomyopathy

0%

(B) Anomalous left coronary artery from the pulmonary artery

0%

(C) Brugada syndrome

0%

(D) Wolf Parkinson White

(E) Jervell and Lange-Nielsen syndrome

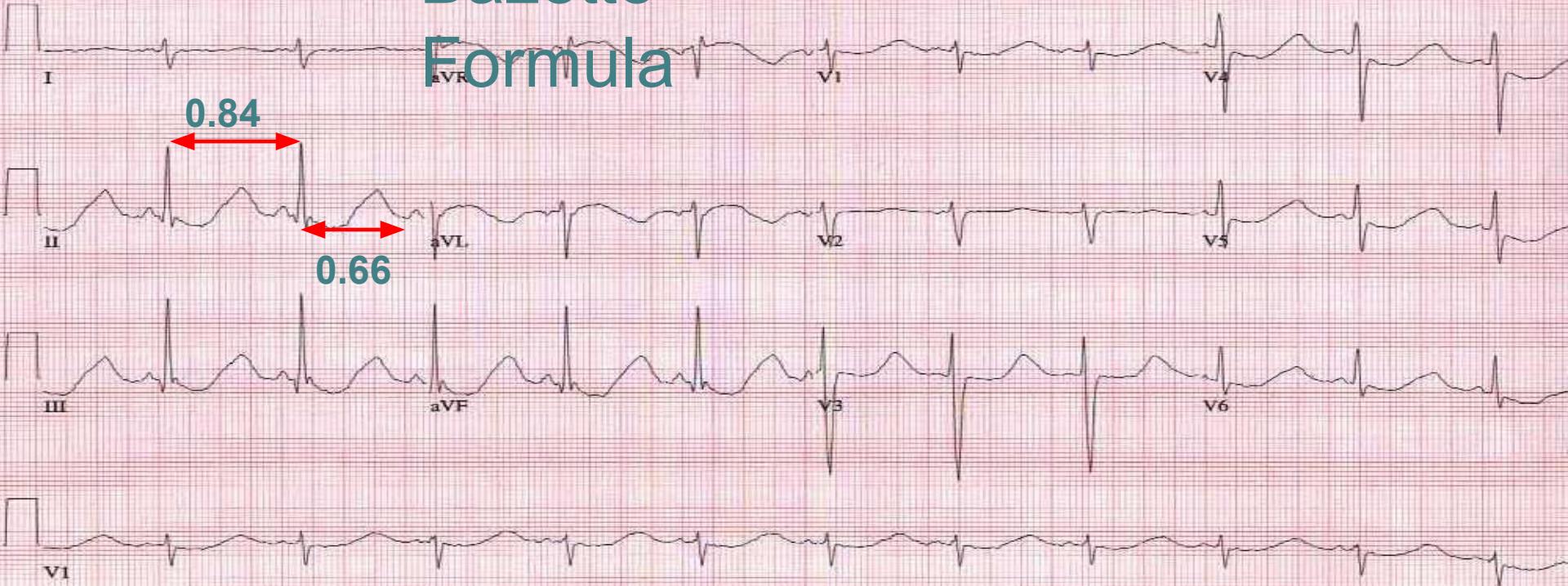
20 yr
Female Caucasian

Room:ICU S
Loc:2

Technician: 02

$$QTc = \frac{QT(\text{sec})}{\sqrt{\text{R-R (sec)}}} = 0.66 / \sqrt{0.84} = 0.72$$

Bazette Formula



Jervell and Lange-Nielsen syndrome

- Deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.
- Autosomal recessive
- Profound bilateral sensorineural hearing loss and long QTc, usually greater than 500 msec.

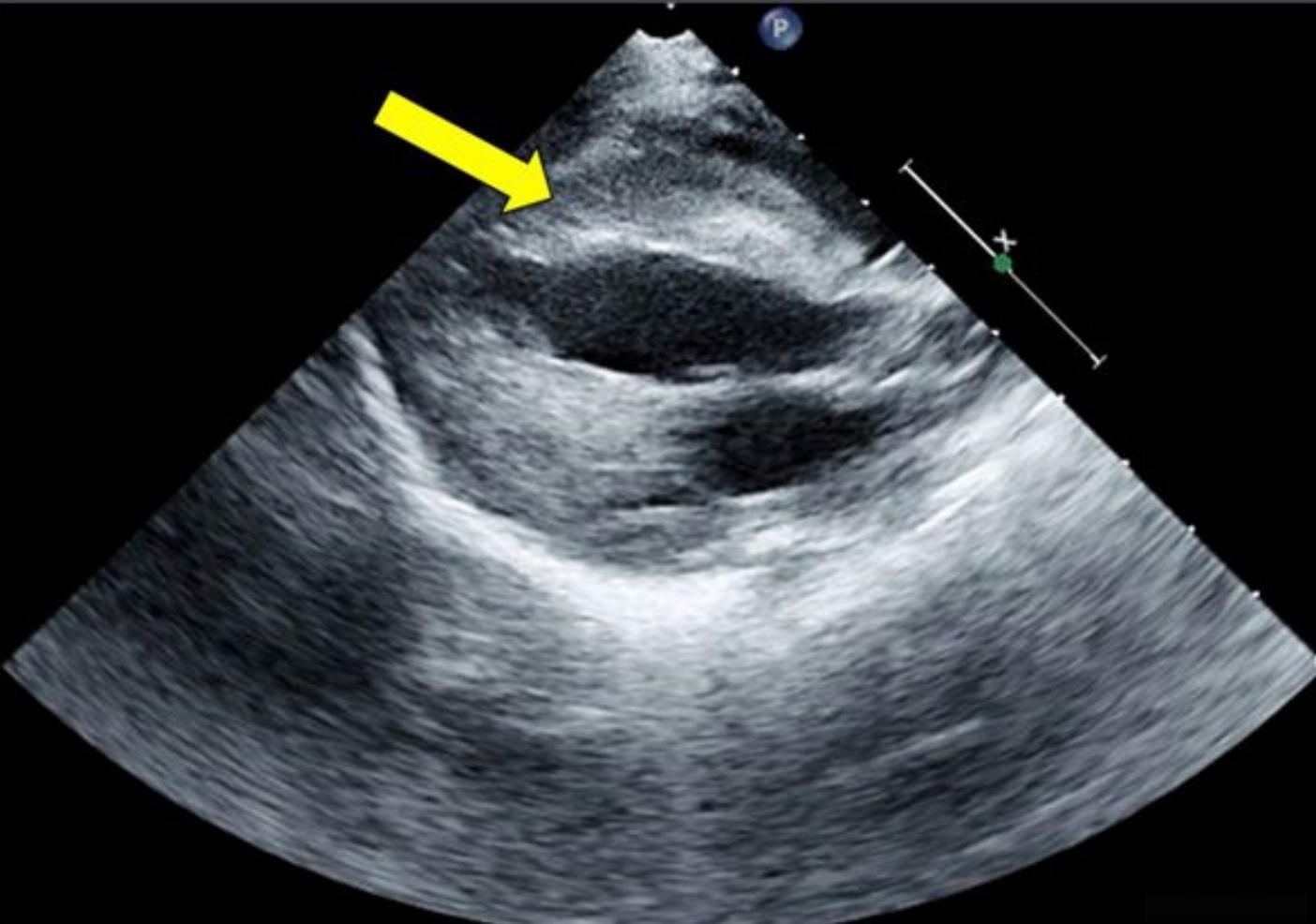
Romano-Ward syndrome

- Autosomal Dominant, and not associated with deafness.

Case #11

- ♥ Large tongue, flabby muscles, cardiomegaly, and the following EKG.





Which of the following is the most likely diagnosis?

- 0% (A) Wolf-Hirschorn
- 0% (B) Waardenburg
- 0% (C) Pompe's
- 0% (D) Beckwith-Wiedemann
- 0% (E) Cri-Du-Chat

Pompe Disease

- SR glycogen storage disorder with deficiency of the enzyme acid a-glucosidase
- Infantile-onset form characterized by hypotonia, cardiomegaly, and hepatomegaly
- Specific EKG, echocardiography, and muscle biopsy findings.
- Enzyme replacement therapy has greatly transformed the quality of life and survival of

Thank you!

