Common Genetic Disorders in Primary Care

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Greenwood Genetic Center
Where Compassion Inspires Progress

Disclosures

- *I perform consulting work for Sanofi, Horizon Therapeutics, and Illumina*

- Founding Member and Treasurer of the Society of PAs in Genetics and Genomics (SPAGG)
- Serve on the Planning Committee for the Clinical Genetics Advanced Practice Provider (CGAPP) Conference
- Serve on the Workforce Development and Optimization Committee and Membership Committee for the American College of Medical Genetics and Genomics (ACMG)

Mission

- Established in 1974, the Greenwood Genetic Center (GGC) is a nonprofit institute, organized to provide clinical genetic services and laboratory testing, to develop educational programs and materials, and to conduct research in the field of medical genetics.

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PAs at the GGC

Jonathon

Laura

Wesley

Educational Objectives

- At the conclusion of this session, the participants should be able to:
  - Examine the genetic etiology of common genetic disorders seen in primary care
  - Discuss frequency, common findings, and management of common genetic disorders
  - Understand the distinctive features associated with these disorders

Common Disorders

- Marfan syndrome
- Neurofibromatosis type 1
- Klinefelter syndrome
- Turner syndrome
- Familial hypercholesterolemia

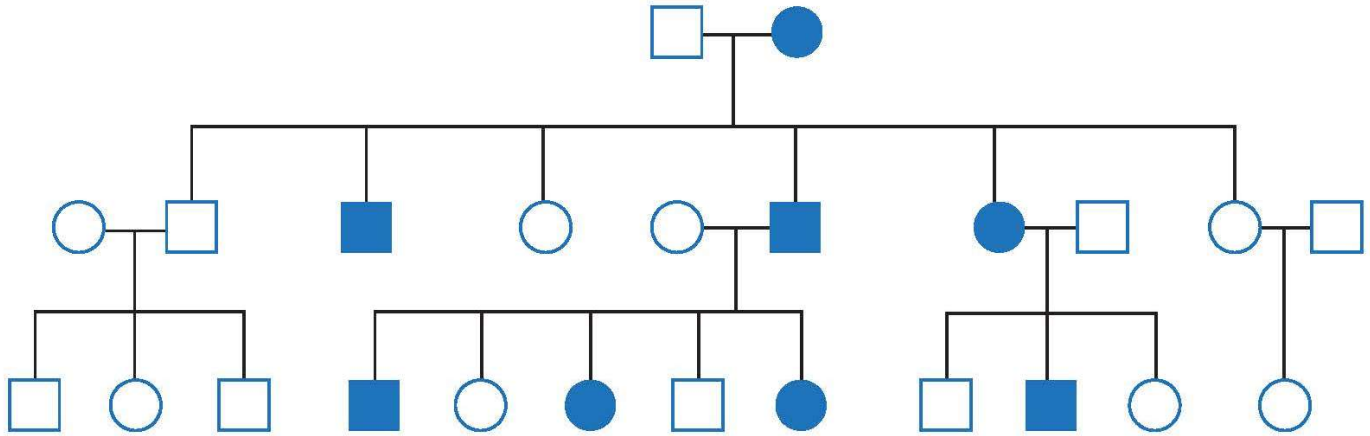
Common Disorders

- **Marfan syndrome**
- Neurofibromatosis type 1
- Klinefelter syndrome
- Turner syndrome
- Familial hypercholesterolemia

Marfan Syndrome

- Inheritance Pattern: autosomal dominant
  - 75% inherited; 25% *de novo*
- Cause: pathogenic variants in the *FBN1* gene. Codes for fibrillin, which is a protein that ultimately provides strength and flexibility to connective tissue.
- Frequency: 1:5,000 people worldwide
- Diagnosis: sequencing analysis of the single gene or multigene panel plus clinical support

Autosomal Dominant Inheritance

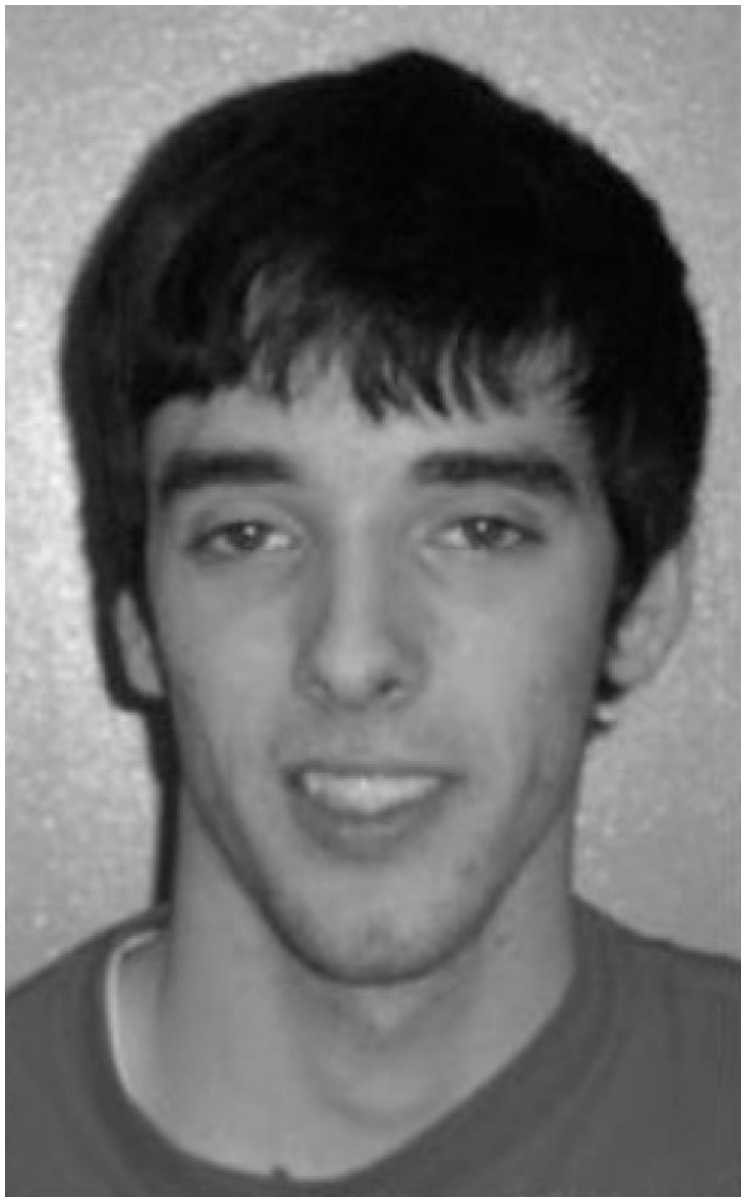


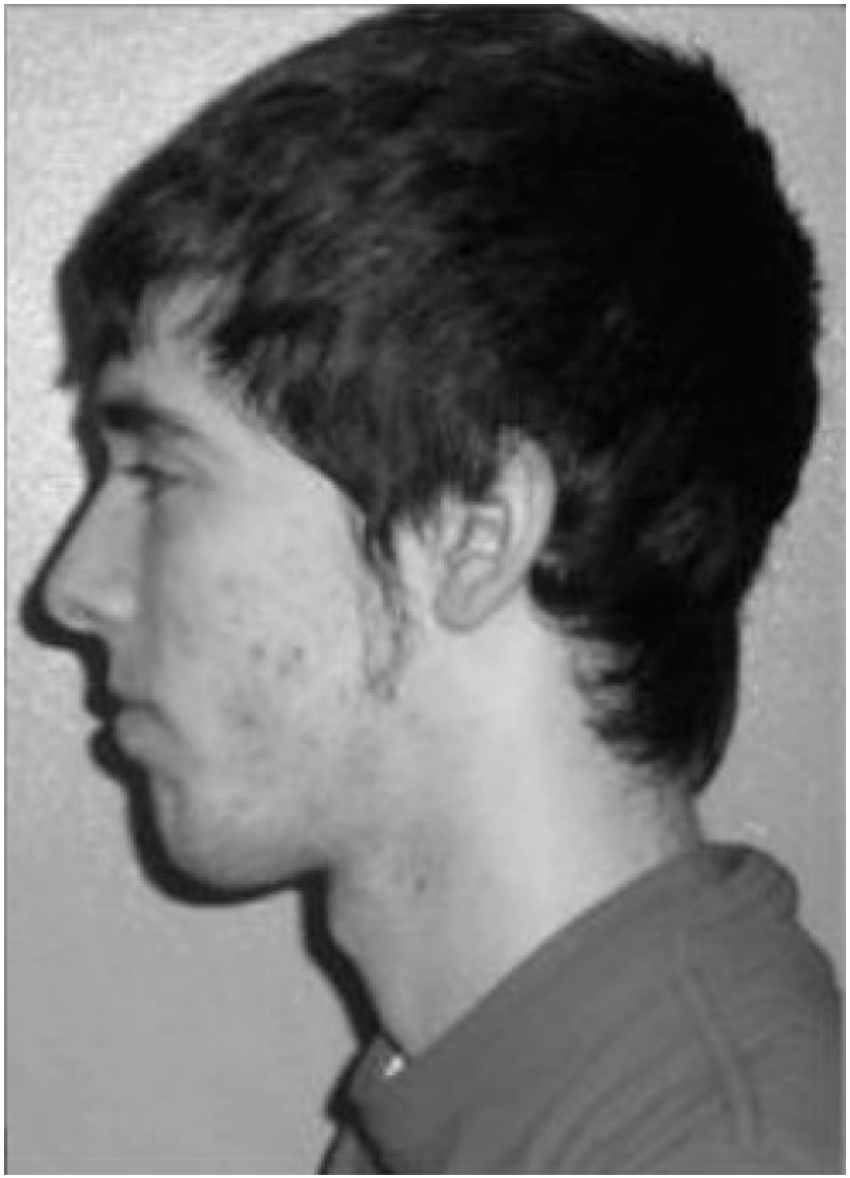
Characteristics of Autosomal Dominant Inheritance

- Multiple generations are affected.
- Males and females are equally likely to be affected.
- Male to male transmission occurs.
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected.

Common Findings

- Tall and slender build
- Disproportionately long arms, legs and fingers
- Pectus carinatum/excavatum
- Spontaneous pneumothorax
- High-arched palate and crowded teeth
- Heart murmurs (aortic root dilatation, mitral valve prolapse)
- Extreme nearsightedness or lens dislocation (ectopia lentis)
- Scoliosis
- Flat feet

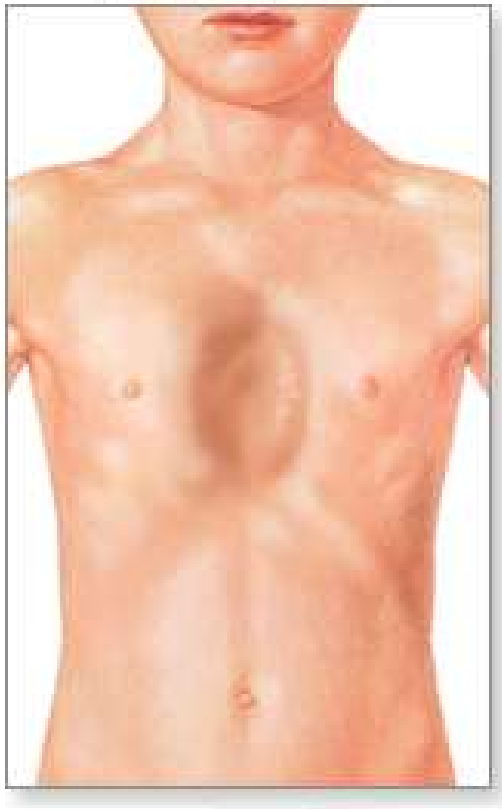




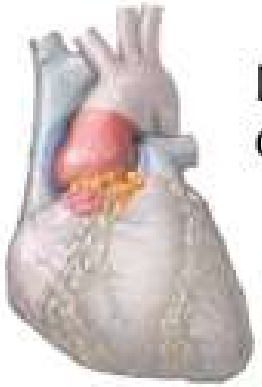
Classical facial features: dolichocephaly, downslanting palpebral fissures, malar hypoplasia, retrognathia

Tinkle et al. 2013

Pectus excavatum

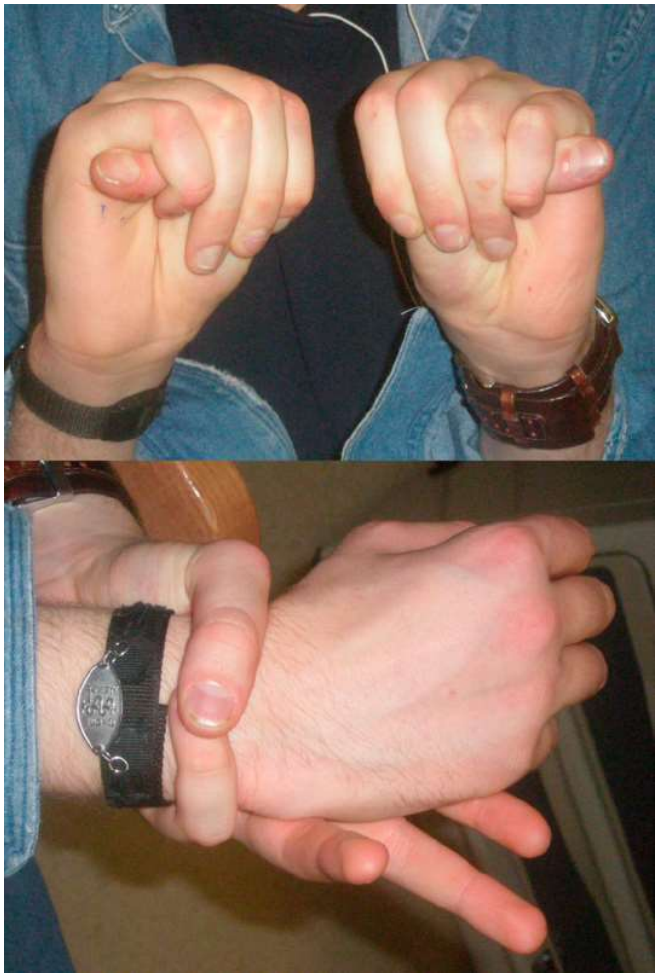


arachnodactyly



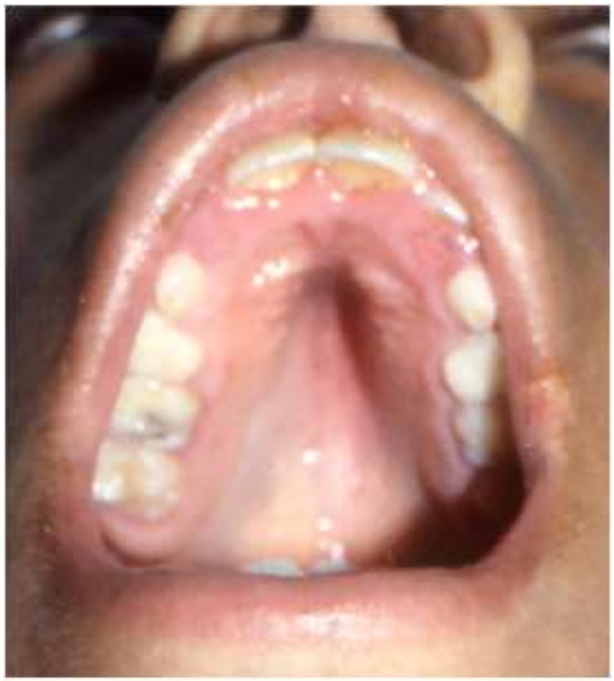
Dilation of aorta

A.D.A.M.

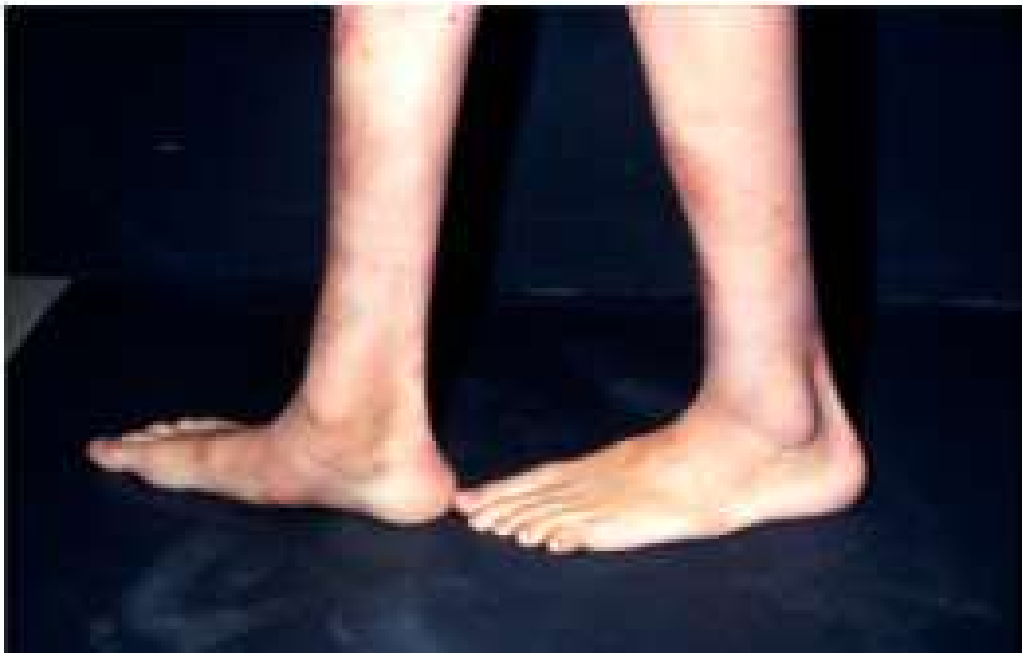


Thumb sign (Steinburg) and wrist sign (Walker)

Tinkle et al. 2013

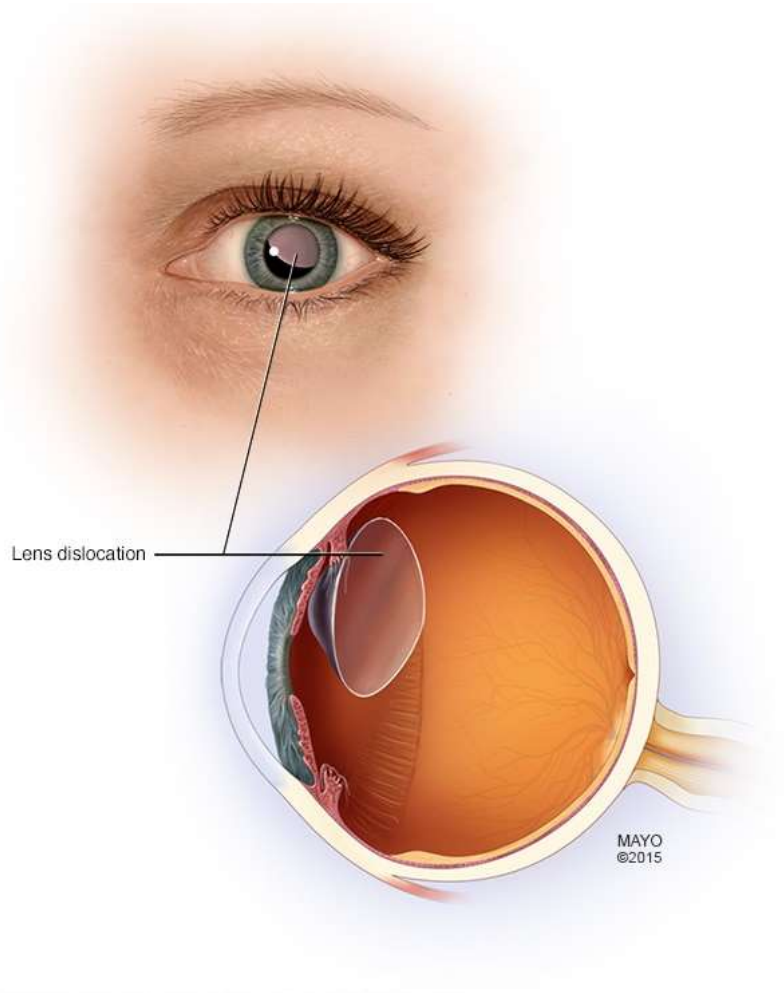


High-arched palate



Hindfoot deformity
(extreme pes planus)

Tinkle et al. 2013



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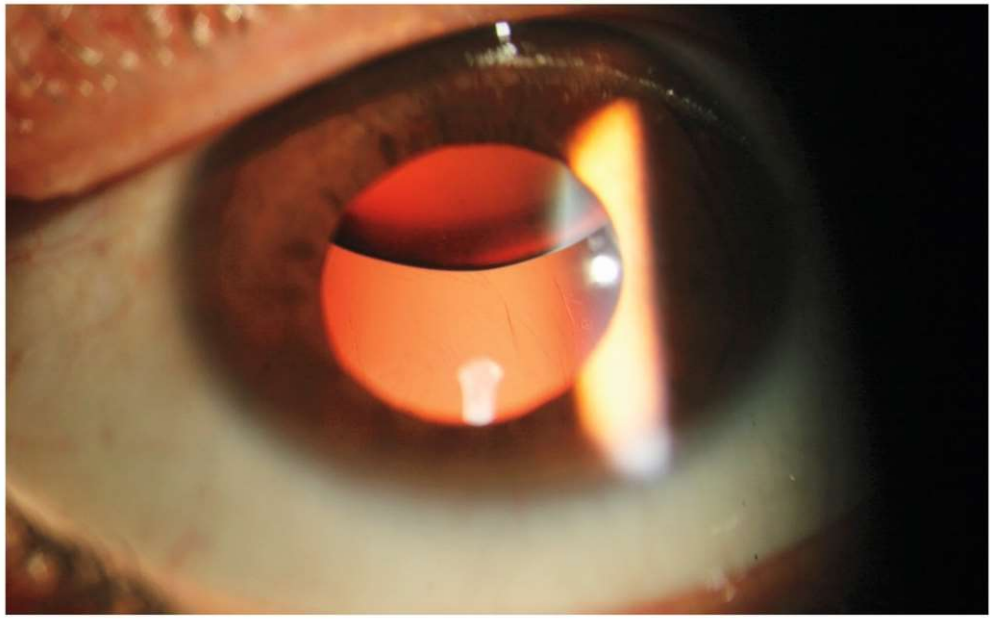


Images from Google Images

Revised Ghent-2 Criteria for the Diagnosis of Marfan Syndrome

- In the absence of a family history:
  - Aortic root dilatation Z score ≥ 2 AND ectopia lentis = Marfan syndrome
  - Aortic root dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome
  - Aortic root dilatation Z score ≥ 2 AND systemic score ≥ 7pts = Marfan syndrome
  - Ectopia lentis AND FBN1 with known aortic root dilatation = Marfan syndrome
- In the presence of a family history:
  - Ectopia lentis AND family history of Marfan syndrome (as defined above)
  - Systemic score ≥ 7 points AND family history of Marfan syndrome (as defined above)
  - Aortic root dilatation (Z ≥ 2 above 20 years old, ≥ 3 below 20 years) AND family history of Marfan syndrome (as defined above)
- Systemic Score (score ≥ 7 indicates systemic involvement)
  - Wrist AND thumb sign - 3 points (wrist OR thumb sign - 1 point)
  - Pectus carinatum deformity - 2 points (pectus excavatum or chest asymmetry - 1 point)
  - Hindfoot deformity - 2 points (plain pes planus - 1 point)
  - Pneumothorax - 2 points
  - Dural ectasia - 2 points
  - Protrusio acetabuli - 2 points
  - Reduced upper segment/lower segment AND increased arm/height AND no severe scoliosis - 1 point
  - Scoliosis or thoracolumbar kyphosis - 1 point
  - Reduced elbow extension - 1 point
  - Facial features (3/5) - 1 point (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
  - Skin striae - 1 point
  - Myopia > 3 diopters - 1 point
  - Mitral valve prolapse (all types) - 1 point

Marfan Syndrome

- Referrals: cardiology, genetics, ophthalmology
- Referrals to consider: cardiothoracic surgery, orthopedics, physical therapy

- Management:
  - Yearly cardiac exam with echocardiogram and ECG
  - Beta blocker or angiotensin receptor blockers to reduce hemodynamic stress on the aortic wall
  - Yearly eye exam

- Care Guide:
  - Health Supervision for Children With Marfan Syndrome

Anticipatory Guidance

TABLE 4 Anticipatory Guidance in Marfan Syndrome

Option	At Diagnosis	0–12 mo	1–5 y	6–12 y[a]	13–18 y[a]	19–22 y
Cardiac examination[b]	√	Each visit	Each visit	Each visit	Yearly	Yearly
Echocardiogram	√	As indicated	Yearly	Yearly	Yearly	Yearly
Ocular (ophthalmology)	√		Yearly	Yearly	Yearly	Yearly
Musculoskeletal[b]						
Scoliosis clinical examination	√	Each visit	Yearly	Every 6 mo	Every 6 mo	Yearly
Joint laxity	√	Each visit	Yearly	Every 6 mo	Every 6 mo	
Pectus deformity	√	Each visit	Yearly	Every 6 mo	Every 6 mo	
Bone age				√[c]		
Review diagnosis	√	PRN	PRN	PRN[d]	PRN[d]	PRN[d]
Examine family members	√	PRN	PRN	PRN	PRN	PRN
Support group information	√	PRN	PRN	PRN	PRN	PRN
Genetic counseling	√				√[e]	√[e]
Lifestyle[f]				√	√	√
Transition					Discuss plans	Begin transition

Many systems should be reviewed regularly at developmentally appropriate stages. PRN, as needed.

[a] Periods of rapid growth require closer supervision.

[b] If abnormal results on examination, refer for further evaluation. Follow-up evaluations as indicated.

[c] Bone age determination in preadolescence. If large discrepancy between bone age and height age, hormonal therapy should be considered.

[d] Review symptoms of potential catastrophic events such as aortic dissection, vision changes, and pneumothorax.

[e] Discuss reproductive and pregnancy risks.

[f] Review physical activity restrictions/lifestyle modifications.

Tinkle et al. 2013

Common Disorders

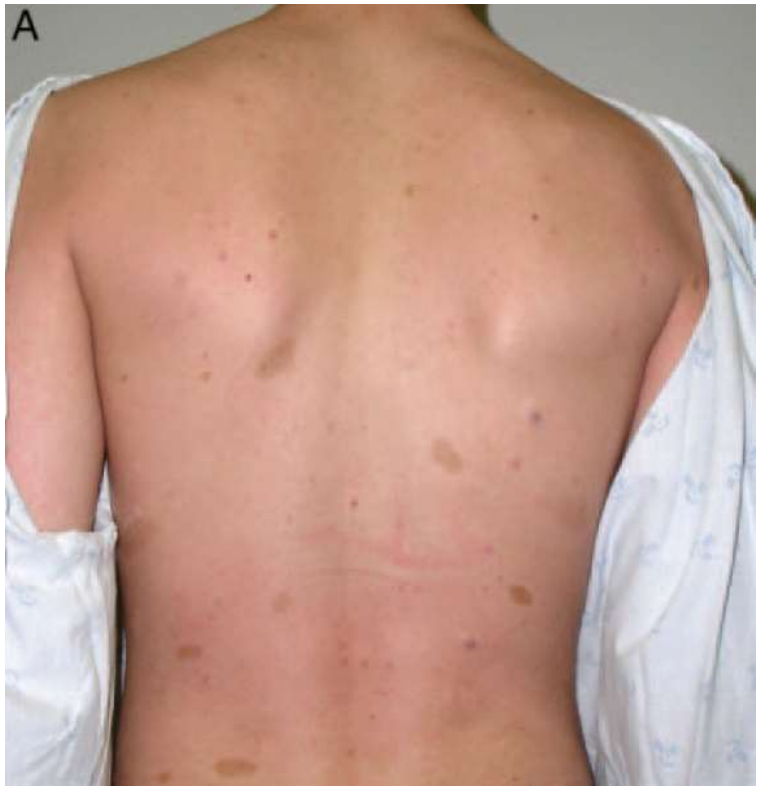
- Marfan syndrome
- **Neurofibromatosis type 1**
- Klinefelter syndrome
- Turner syndrome
- Familial hypercholesterolemia

Neurofibromatosis 1

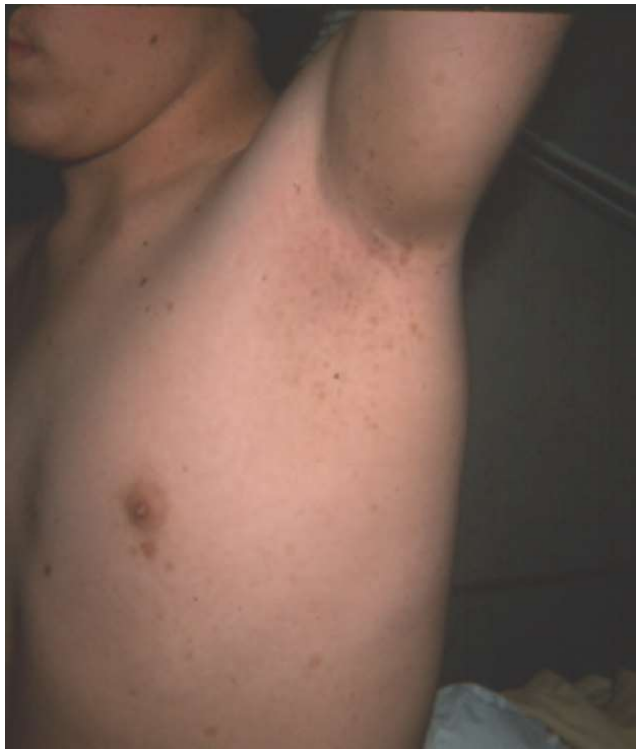
- Inheritance Pattern: autosomal dominant
  - 50% inherited; 50% *de novo*
- Cause: pathogenic variants in the *NF1* gene. Codes for neurofibromin, a protein that acts as a tumor suppressor.
- Frequency: 1:3,000 people worldwide
- Diagnosis: sequencing and deletion/duplication analysis of the single gene plus clinical support

Common Findings

- Café-au-lait macules
- Neurofibromas
- Short stature
- Macrocephaly (large head)
- Axillary or groin freckling
- Scoliosis
- Learning difficulties

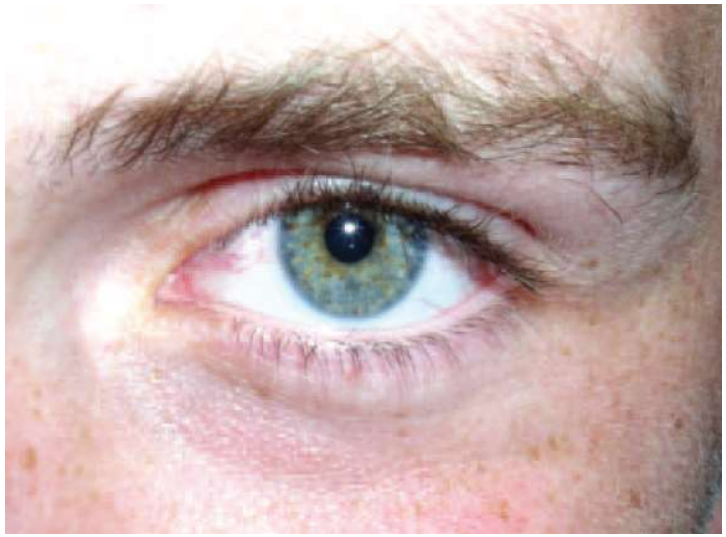


Café-au-lait macules

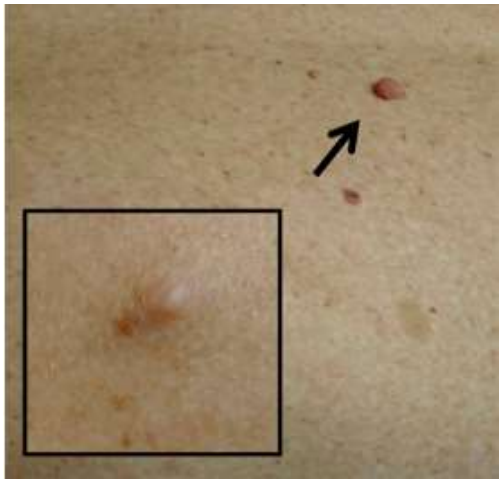


Axillary freckling

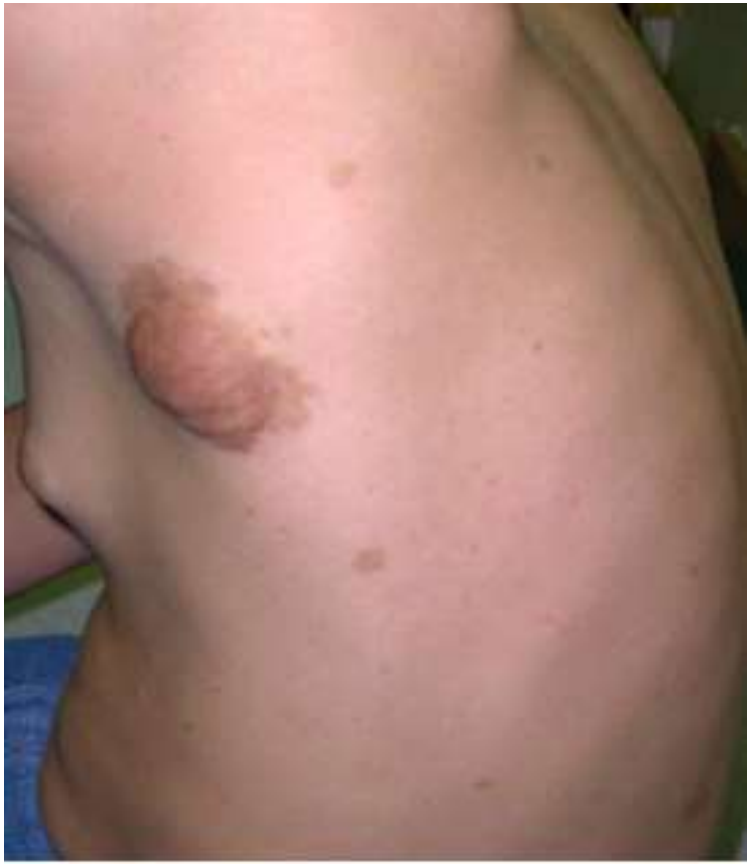
Lisch nodules



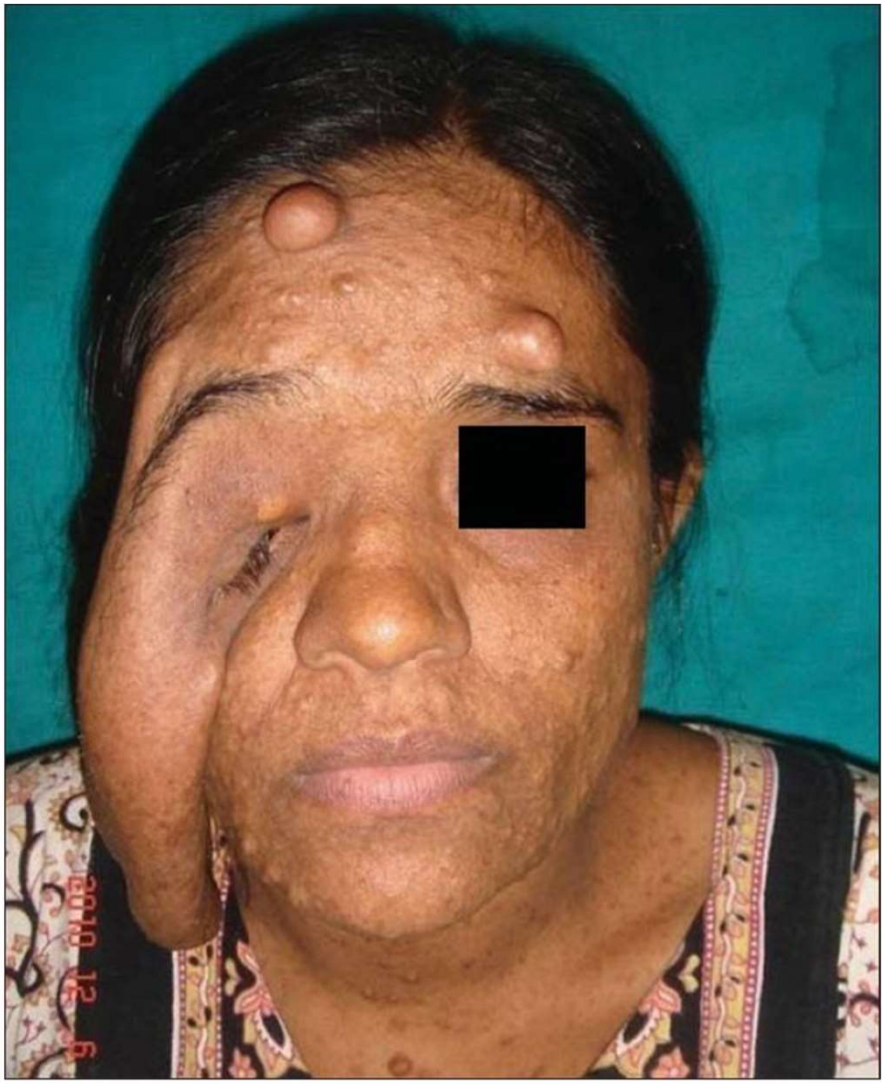
Neurofibroma



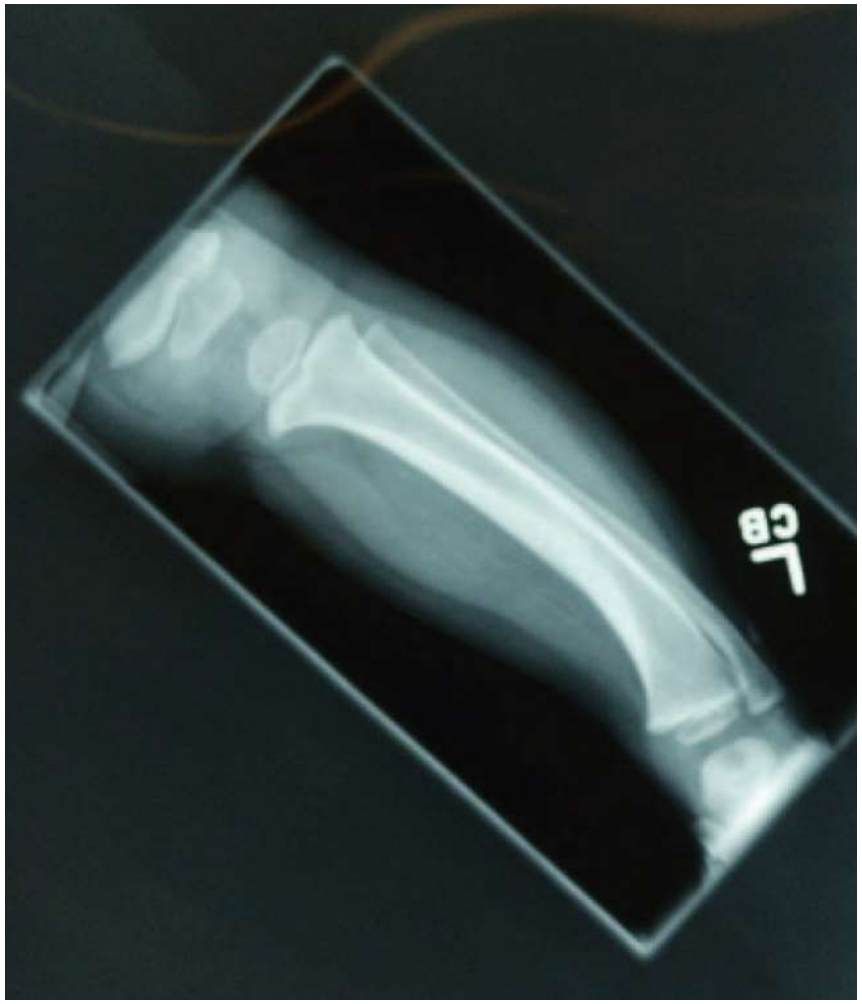
Miller et al. 2019



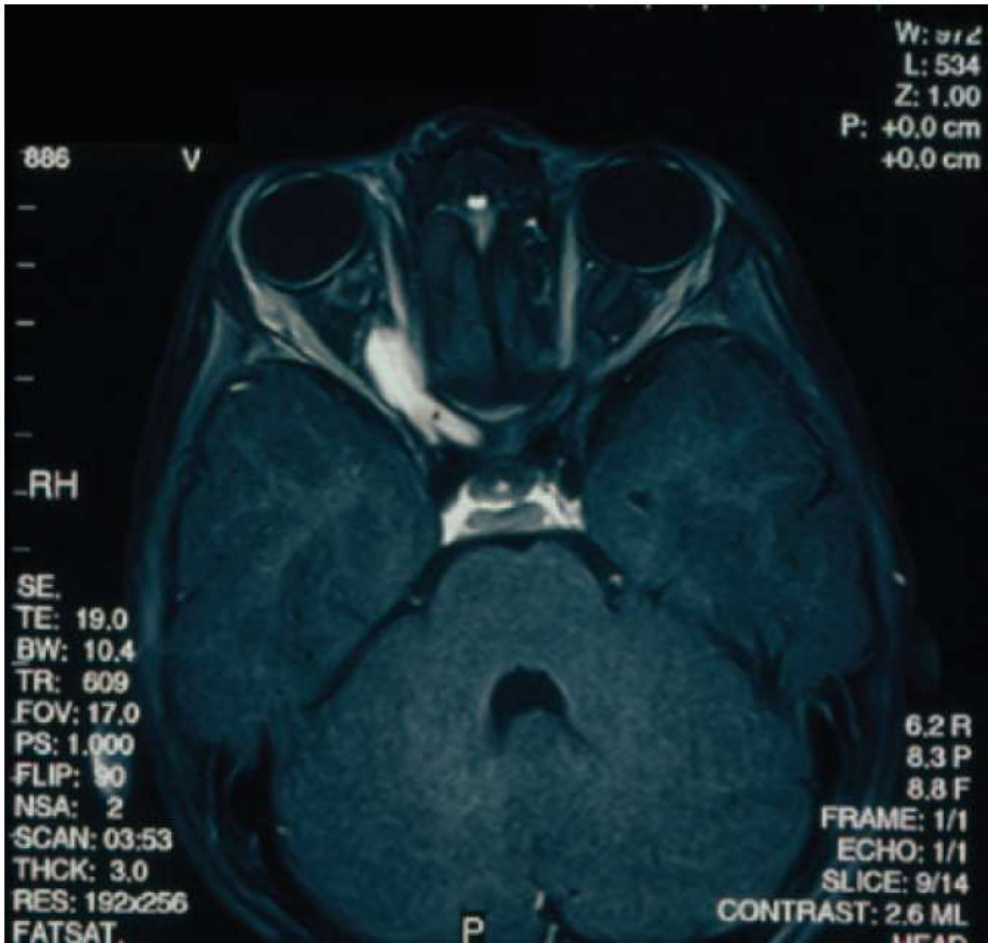
Plexiform neurofibroma
(Miller et al. 2019)



Facial plexiform neurofibroma
(Image from IDOJ)



Bowing of the tibia



Optic glioma

Miller et al. 2019

Diagnostic Criteria for Neurofibromatosis 1

- The presence of 2 or more of the following findings is considered diagnostic:
  - 6 or more café-au-lait macules (>0.5cm in children or >1.5cm in adults)
  - 2 or more cutaneous/subcutaneous neurofibromas or 1 plexiform neurofibroma
  - Axillary or groin freckling
  - Optic pathway glioma
  - 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
  - Body dysplasia (sphenoid wing dysplasia, bowing of the long bone +/- pseudarthrosis)
  - First degree relative with neurofibromatosis 1 as defined by the above criteria

Neurofibromatosis 1

- Referrals: genetics, ophthalmology
- Referrals to consider: developmental pediatrician, neurology, oncology, physical therapy
- Management:
  - Yearly eye exam until age 8 years, then every 2 years after
  - Yearly blood pressure screening
  - Yearly physical exam, including skin and neuro exam
  - Assessing the child's speech and motor skills for deficits that may require further assessment
  - Evaluate for precocious puberty
  - Begin annual mammography in women at age 30 years
- Care Guide:
  - Health Supervision for Children With Neurofibromatosis

Anticipatory Guidance

TABLE 4 Health Supervision Guidelines for Children With NF1

	Infancy, 1 mo to 1 y	Early Childhood, 1–5 y	Late Childhood 5 y to Puberty	Adolescence and Young Adulthood (Postpubertal)
Genetic counseling				
Genetic etiology	X[a]	—	—	X[b]
Genetic testing	As needed[c]	As needed[c]	As needed[c]	As needed[c]
Future reproductive planning	X[a]	—	X[b]	X[d]
Medical evaluation and treatment[e]				
Monitor growth rate	X	Annual	Annual[f]	Annual
Measure head circumference	X	X	X	—
Blood pressure	—	Annual	Annual[f,g]	Annual[f]
Attention to cardiac examination	X	—	—	—
Skin examination	X	Annual	Annual	Annual
Bone examination or scoliosis examination	X[b]	Annual	Annual[f]	Annual[f]
Neurologic examination	X	Annual	Annual[f]	Annual[f]
Ophthalmologic examination	Annual	Annual	Annual	As needed
Monitor precocious puberty	—	Annual[f]	Annual[f]	—
Diagnostic imaging examinations[e]	As needed[e]	As needed[e]	As needed[e]	As needed[e]
Developmental and psychosocial evaluation[g]	X	X	X	X
Anticipatory guidance; phenotype review[h]	X[a]	X[b]	X[b]	X[b]
Family support	X	X	X	X
Support groups	X	X	X[b]	X[b]
Long-term planning	X	X	X[b]	X[b]
Sexual and reproductive issues	—	—	X[b]	X

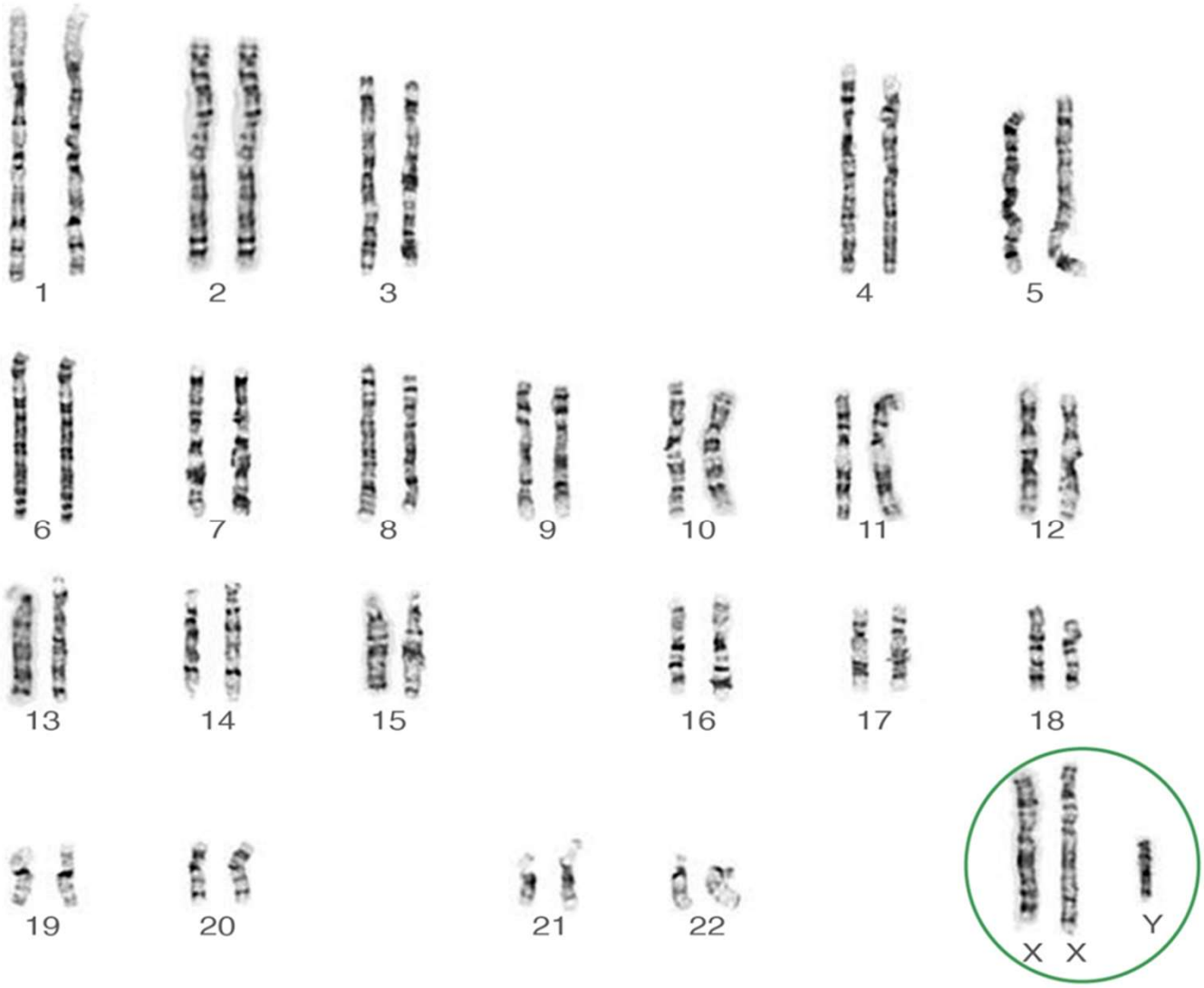
Common Disorders

- Marfan syndrome
- Neurofibromatosis type I
- **Klinefelter syndrome**
- Turner syndrome
- Familial hypercholesterolemia

Klinefelter Syndrome (XXY)

- Inheritance Pattern: random error (nondisjunction) resulting in an extra sex chromosome (X)
- Frequency: 1:500 – 1000 newborn males
  - One of the most common sex chromosome disorders
- Diagnosis: karyotype analysis (chromosomes)

Klinefelter Syndrome Karyotype - 47,XXY



Chromosomes artificially straightened for illustrative purposes causing some apparent discrepancies in banding patterns of chromosome pairs

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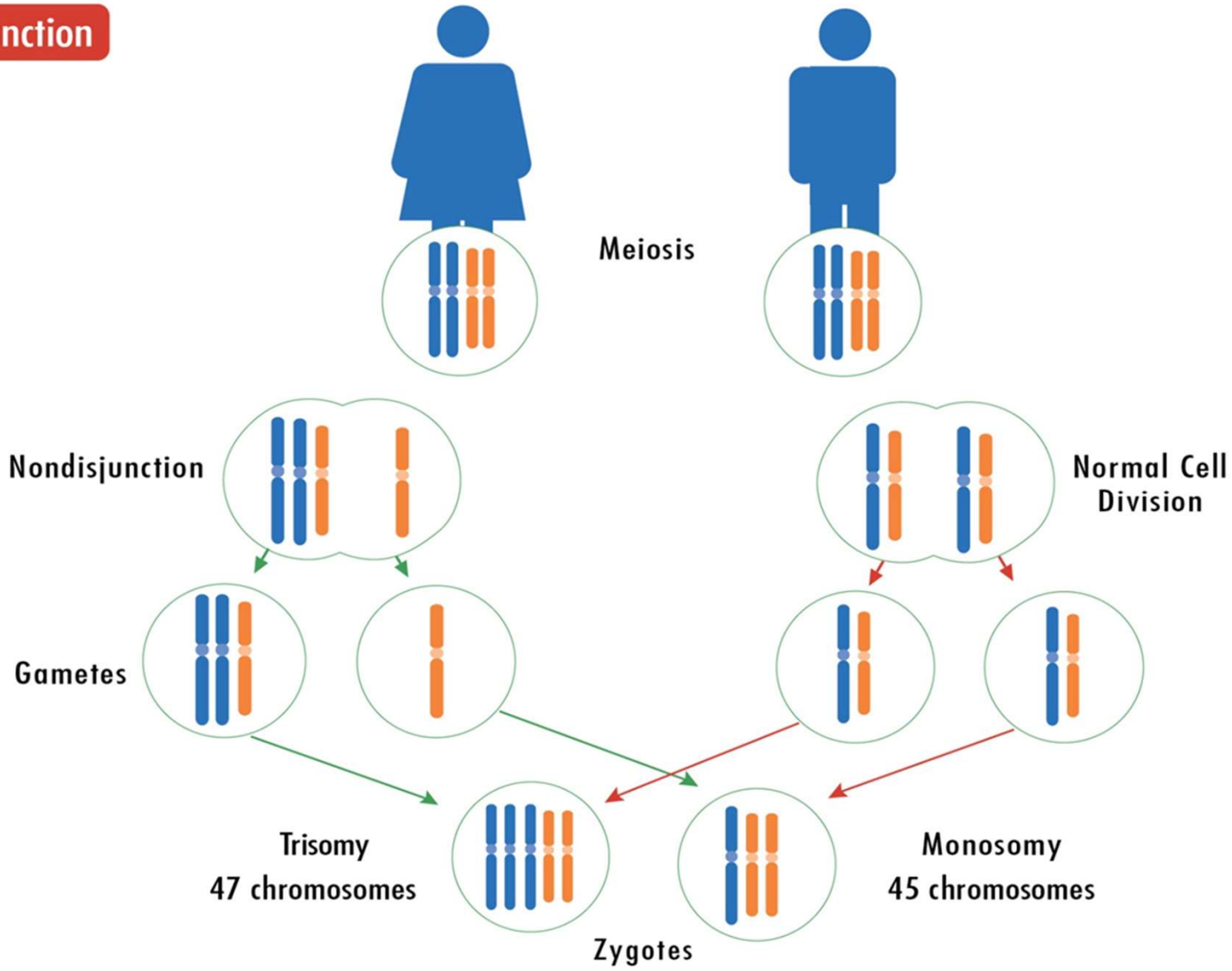
Nondisjunction



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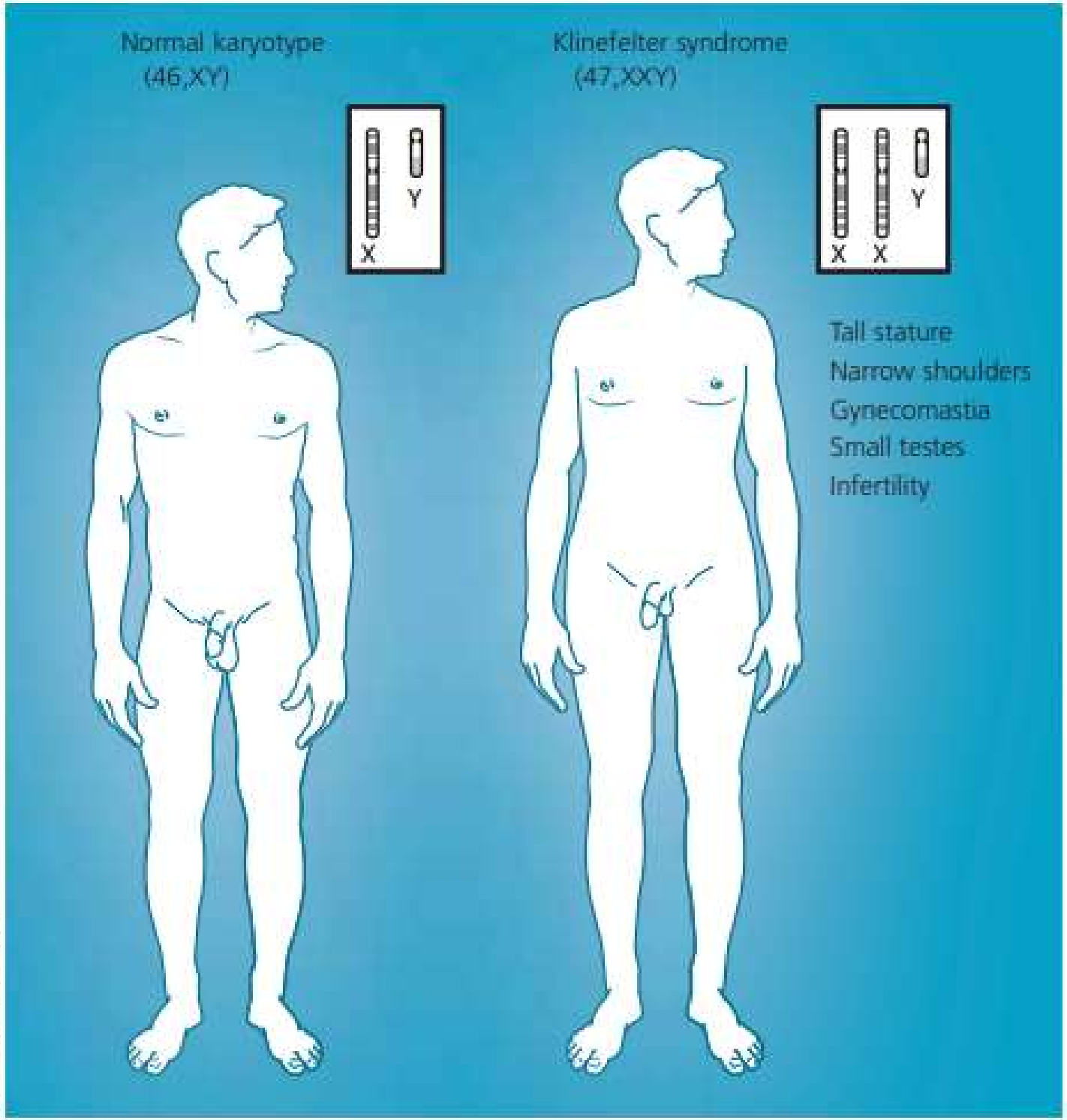

Wattendorf & Muenke 2005

Klinefelter Syndrome

- Referrals: developmental pediatrics, endocrinology, genetics
- Management:
  - At diagnosis, a comprehensive neurodevelopmental evaluation
    - Evaluate for learning difficulties especially expressive language, reading, and spelling
    - Evaluate for behavior problems, immaturity, and poor psychosocial adjustment
  - Androgen (testosterone) replacement therapy should be initiated when there is laboratory evidence of a testosterone deficit or when hypergonadotropism is present (usually around puberty; 12 to 14 years old)
- Care Guide:
  - Klinefelter Syndrome Review - American Academy of Family Physicians

Common Disorders

- Marfan syndrome
- Neurofibromatosis type I
- Klinefelter syndrome
- **Turner syndrome**
- Familial hypercholesterolemia

Turner Syndrome

- Inheritance Pattern: usually *de novo* due to a random event (nondisjunction) resulting in a missing or partially missing sex chromosome (X)
- Frequency: 1:2,500 newborn girls but more common in pregnancies that do not survive to term
- Diagnosis: karyotype analysis

Monosomy X - Turner Syndrome 45,X

Chromosomes artificially straightened for illustrative purposes causing some apparent discrepancies in banding patterns of chromosome pairs

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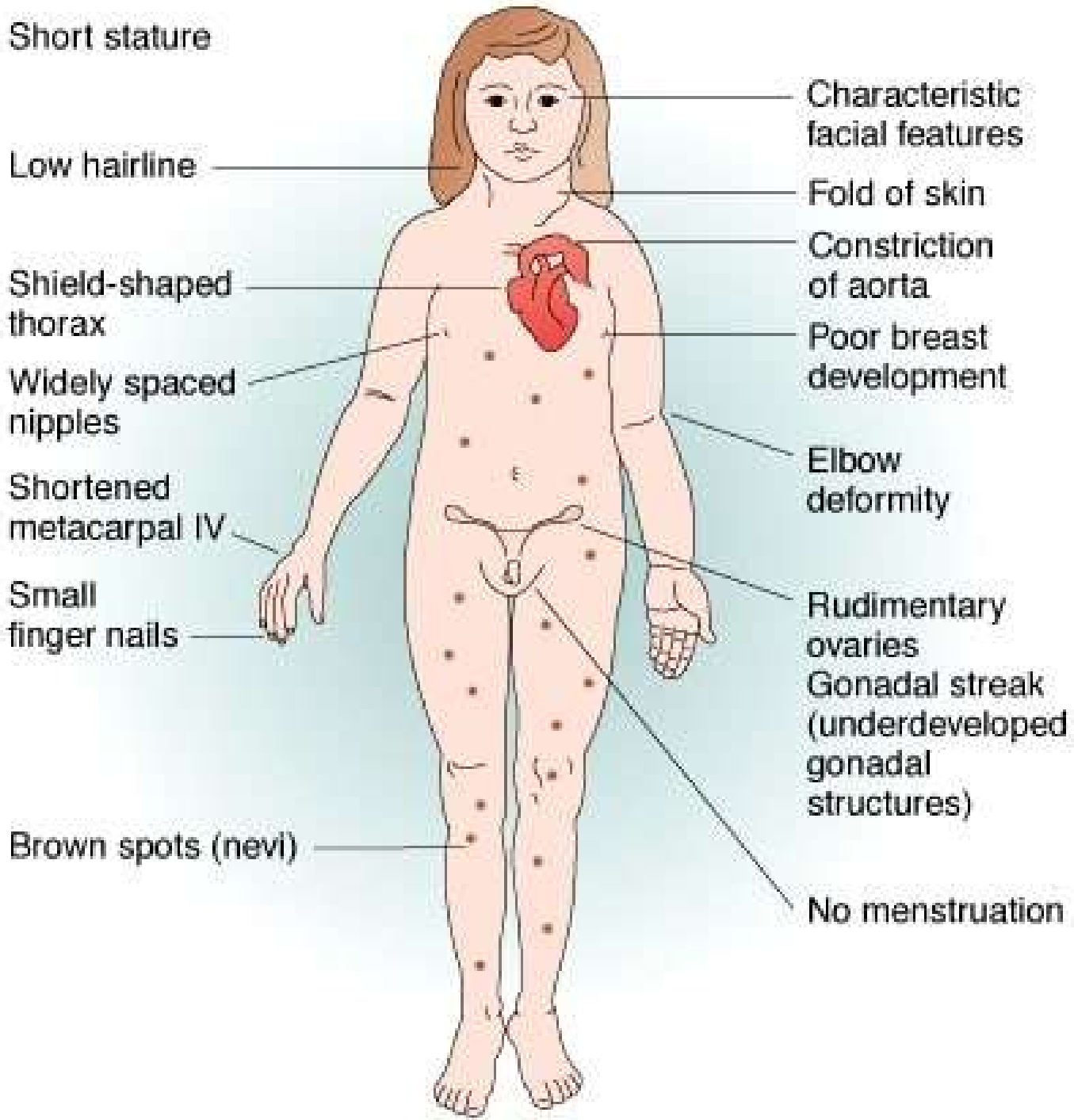
Common Findings

- Short stature
- Webbed neck
- Low posterior hairline
- Distinctive facies (epicanthal folds, downslanting palpebral fissures, low-set and prominent ears and micrognathia)
- Congenital lymphedema (cystic hygroma may be seen prenatally)
- Broad chest with widely spaced nipples
- Congenital heart defects (commonly coarctation of the aorta)
- Renal anomalies (commonly horseshoe kidney)
- Ovarian dysgenesis
- Learning disabilities especially in math and visual-spatial relationships
- Intellectual disability present in 10% of individuals


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

Turner Syndrome

- Referral: audiology, cardiology, endocrinology, genetics
- Management:
  - Echocardiogram, renal ultrasound, hearing test, labs (TSH, lipids, LFTs, A1C, vitamin D, celiac screening)
  - Estrogen replacement therapy for feminization in adolescent females
  - See next slide for more details
- Care Guide:
  - Clinical Practice Guidelines for the Care of Girls and Women with Turner syndrome

Table 6 Recommendations for screening in Turner syndrome at diagnosis and throughout life (excluding those covered elsewhere, i.e. cardiac and neuropsychological).

	At diagnosis	**After diagnosis** (childhood)	**After diagnosis** (adults)
Weight/BMI	Yes	Every visit	Every visit
Blood pressure	Yes	Every visit	Every visit
Thyroid function (TSH and (free) T4)	Yes	Annually	Annually
Lipids			Annually if at least one cardiovascular risk factor[¤] or regional recommendation
Aminotransferase, GGT and alkaline phosphatase		Annually after 10 years of age	Annually
HbA1c with or without fasting plasma glucose		Annually after 10 years of age	Annually
25-Hydroxyvitamin D		Every 2–3 years after 9–11 years of age	Every 3–5 years
Celiac screen		Starting at 2 years; thereafter every two years	With suggestive symptoms
Renal ultrasound	Yes		
Audiometric evaluation	Yes*	Every 3 years	Every 5 years
Ophthalmological examination	Yes[#]		
Dental evaluation	Yes, if no previous care has been established		
Clinical investigation for congenital hip dysplasia	Yes, in newborns		
Skin examination	At diagnosis	Annually	Annually
Bone mineral density			Every 5 years and when discontinuing estrogen
Skeletal assessment		5–6 years and 12–14 years (see 6.1.10.)	

The recommendations are for screening only. A clinical suspicion of active disease should always lead to relevant investigation. For details, please see text.

*When 9–12 months old; [#]when 12–18 months old; [¤]cardiovascular risk factors: hypertension, overweight, tobacco, diabetes, and physical inactivity.

Gravholt et al. 2017

Common Disorders

- Marfan syndrome
- Neurofibromatosis type I
- Klinefelter syndrome
- Turner syndrome
- **Familial hypercholesterolemia**

Familial Hypercholesterolemia

- Premature atherosclerotic cardiovascular disease due to lifelong exposure to elevated LDL-C

- Untreated individuals have significant risk for fatal or nonfatal coronary event
  - Males: 50% risk by 50 years
  - Females: 30% risk by 60 years

Familial Hypercholesterolemia

- Inheritance Pattern: autosomal dominant or autosomal recessive
- Cause: pathogenic variants in the *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9* genes
- Frequency: 1:200-250 (~220)
  - Most common genetic cause of cardiovascular disease
- Diagnosis: sequencing analysis of the single gene or multigene panel plus clinical support

Genes and LDL

Gene	Mutant Gene Product	Pattern of Inheritance	Effect of Disease-Causing Mutations	Typical LDL Cholesterol Level (Normal Adults: ≈120 mg/dL)
LDLR	LDL receptor	Autosomal dominant	Loss of function	Heterozygotes: 350 mg/dL Homozygotes: 700 mg/dL
APOB	Apoprotein B-100	Autosomal dominant*	Loss of function	Heterozygotes: 270 mg/dL Homozygotes: 320 mg/dL
LDLRAP1	ARH adaptor protein	Autosomal recessive†	Loss of function	Homozygotes: 470 mg/dL
PCSK9	PCSK9 protease	Autosomal dominant	Gain of function	Heterozygotes: 225 mg/dL

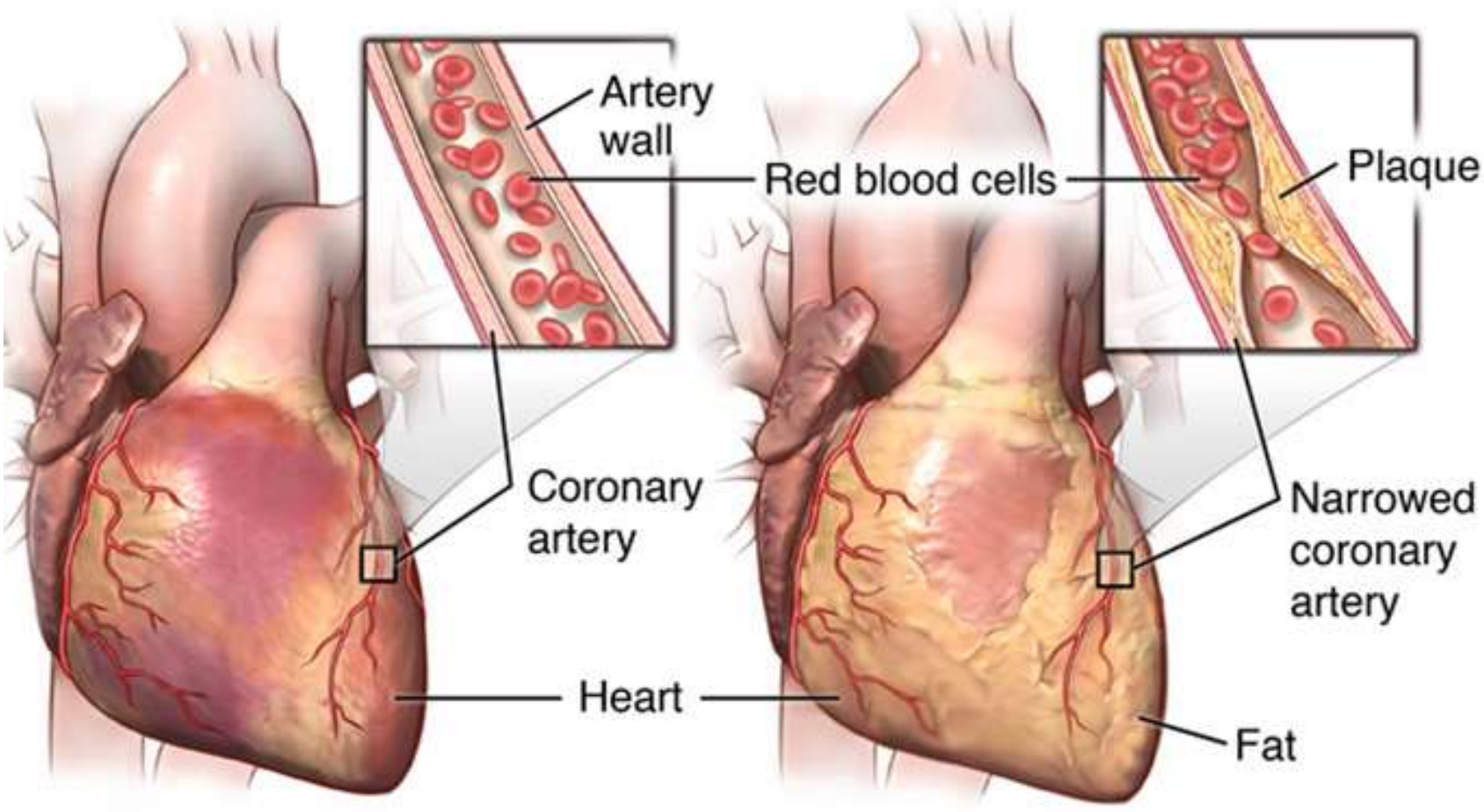
LDL, Low-density lipoprotein.

Thompson and Thompson, 8th edition

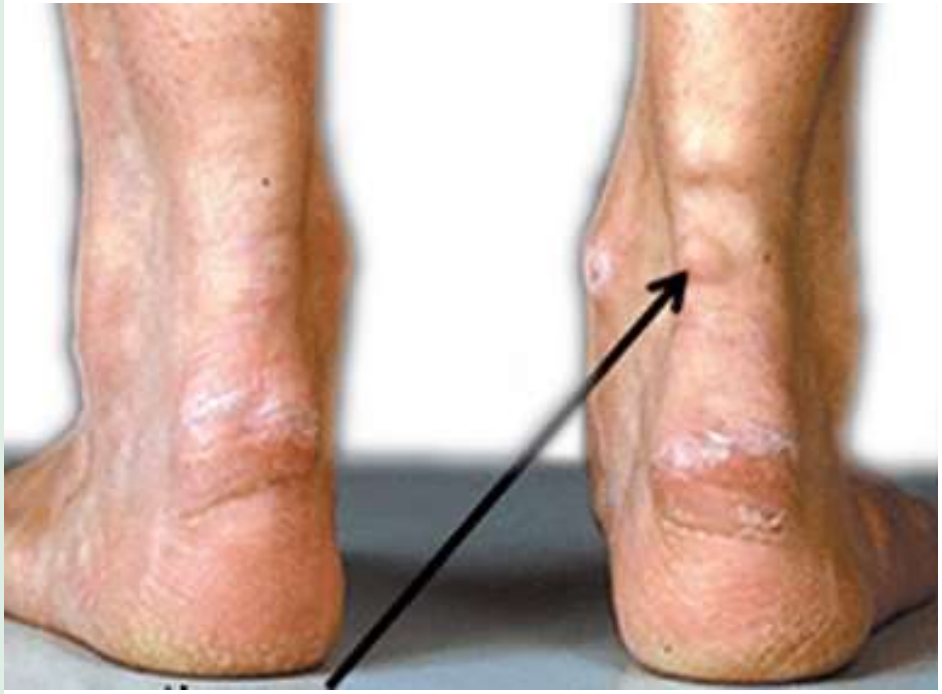
Common Findings

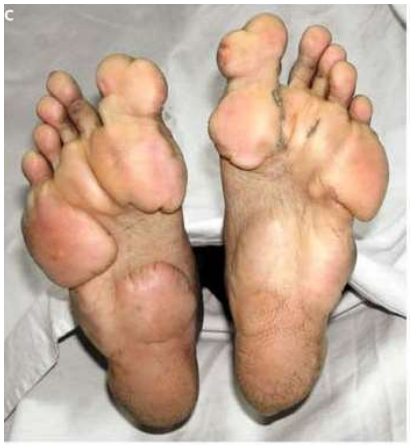
- Severely elevated LDL cholesterol levels that lead to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age
- Xanthomas – patches of yellowish cholesterol buildup (may worsen with age as a result of extremely high cholesterol levels)
  - Occur around the eyelids and within the tendons of the elbows, hands, knees, and feet
- Coronary artery disease (CAD), which may manifest as angina and myocardial infarction; stroke occurs more rarely

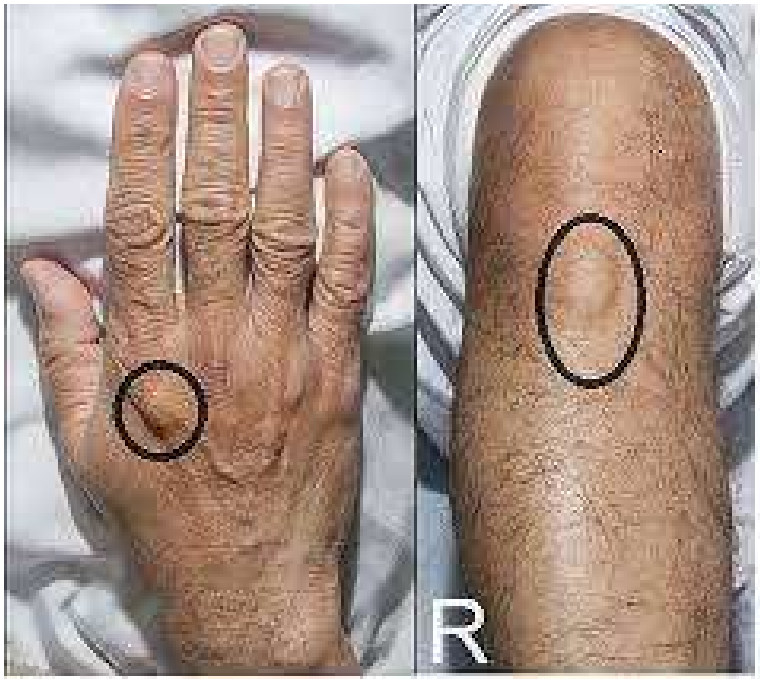
Coronary Artery Disease



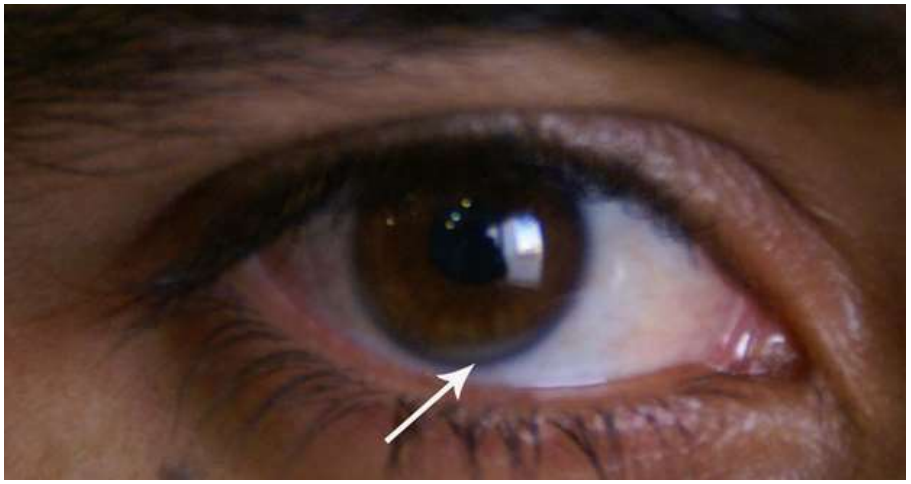
Xanthomas







Corneal Arc



Familial Hypercholesterolemia

- The diagnostic criteria most widely used in Western countries include:
  - Extreme hypercholesterolemia
    - Untreated adults with LDL-C >190 mg/dL or total cholesterol levels >310 mg/dL
    - Untreated children/adolescents with LDL-C levels >160 mg/dL or total cholesterol levels >230 mg/dL)
  - History of premature CAD or other CVD
  - Xanthomas
  - Corneal arcus
  - Family history of features suggestive of FH
  - Genetic testing

Familial Hypercholesterolemia

- Referrals: cardiology/lipid specialist, if needed
- Management:
  - Reduce CAD risk factors: cessation of smoking; regular physical activity; healthy diet; weight control; treatment of hypertension; low-dose aspirin in high-risk individuals; pharmacotherapy (statins with additional medications as needed) to reduce lipid levels
  - Children with FH: referral to a lipid specialist; diet and lifestyle modifications; statins can be used in children starting around age eight years
  - Children and adults homozygous for FH: referral to a lipid specialist or specialized center for management of multiple drug therapy; LDL apheresis is often required; liver transplantation in rare circumstances

Rationale for Genetic Testing

- Presence of increased risk in individuals with pathogenic variants
- Availability of effective treatment to lower LDL-C levels
- Current yields published in literature
- Enhancement of cascade testing with genetic testing
- Likelihood of improved medication compliance

Find Genetics in Your Area

- American College of Medical Genetics and Genomics (ACMG)
  - https://clinics.acmg.net/
- National Society of Genetic Counselors (NSGC)
  - https://findageneticcounselor.nsgc.org/

Genetic Resources

- GeneReviews®
- MedlinePlus (formerly Genetics Home Reference)
- Genetics and Rare Disease Information Center (GARD)
- Online Mendelian Inheritance in Man (OMIM)
- Orphanet

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Huge Thanks to My GGC Family

Questions?

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- SPAGG website: https://spagg.wildapricot.org/