RED FLAGS FOR GENETICS

A 15 minute perspective

Introduction

Carrie Schmid, MD, FAAP, FACMG
Clinical Geneticist
Assistant Professor of Pediatrics and Molecular and Human Genetics, Baylor College of Medicine

Alexandra Grace, CPNP-PC
Certified Pediatric Nurse Practitioner
Instructor of Pediatrics and Molecular and Human Genetics, Baylor College of Medicine

Objectives

1. Define genetic red flags
2. Identify historical findings that should raise a flag
3. Identify physical and lab features that should raise a flag
4. Review genetic referral indications
5. Empower primary care providers to confidently refer to genetics

Why improve recognition in the clinic?

- Understanding a patient's predisposition to a health condition based on historical or clinical details will improve prevention and or early treatment
- Genetic testing is advancing rapidly and patients expect providers to be up-to-date
- Referral to a genetics specialist will allow for selection of appropriate tests, counseling on risks and benefits of testing, counseling on recurrence risks, and development of a surveillance and treatment plan tailored to a patient's genetic condition--"personalized medicine."

What is a Red Flag?

A clinical finding discovered in the history, physical examination, or laboratory studies that suggests the presence of a genetically influenced disease.

This discovery may require further actions, such as referral, counseling, screening, or long-term monitoring.

D. H. Lawrence

"What the eye doesn't see and the mind doesn't know, doesn't exist."

What makes a great well child visit?

All signs of disease or potential risks for disease are detected

... in 15 minutes or less

The primary care provider is presented with a nearly impossible task. They must conduct a thorough history, perform a comprehensive physical exam, deliver detailed anticipatory guidance, and discuss patient and parental concerns.

Ready to escape the exam room?

Goals

01 Put yourself in the position of the primary provider in a busy clinic

02 Follow along on the "key feature" slides to gather at least 2-3 "red flags"

03 Did you escape the well child visit in 15 minutes with a referral to Genetics?

Your MA approaches you

Luke is ready. He's usually seen by your partner. His mom doesn't have concerns. No new medications. And don't forget about the going away lunch starting in 20 minutes.

Time to go and see your 11:30

Quick Chart Review

Past Medical History

- Feeding difficulties
- Developmental delays
- Congenital heart disease

Social History

- Lives with single mother
- Attends daycare
- No tobacco exposure
- No concern for abuse

Family History

- Mother heart problem, learning disability
- Maternal grandfather eye surgery as child, learning disability

VITAL SIGNS

LUKE NOBLE [M]

DOB 8/20/2020, 9 MONTHS

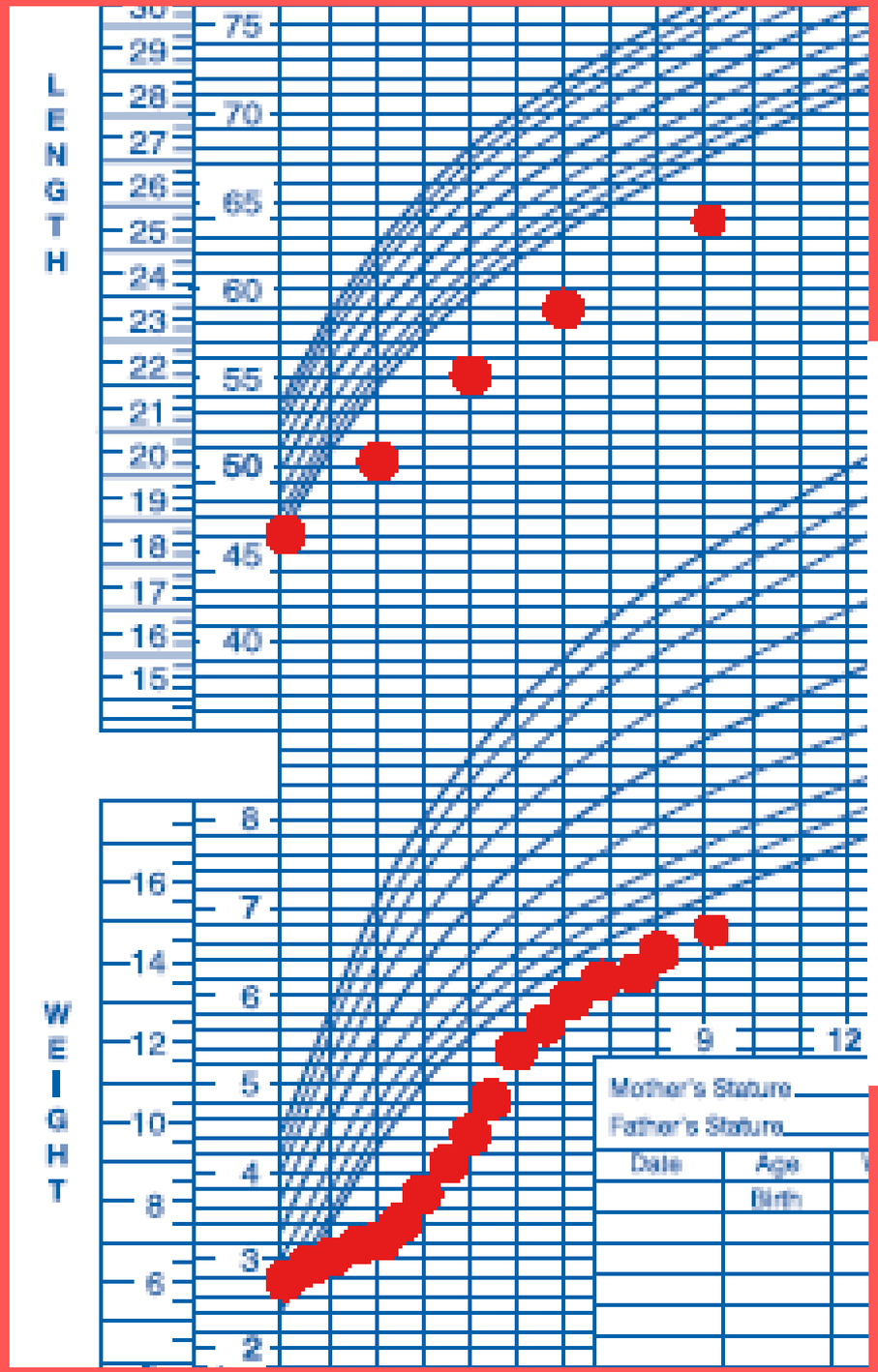
HT: 64 CM (<2ND%TILE)

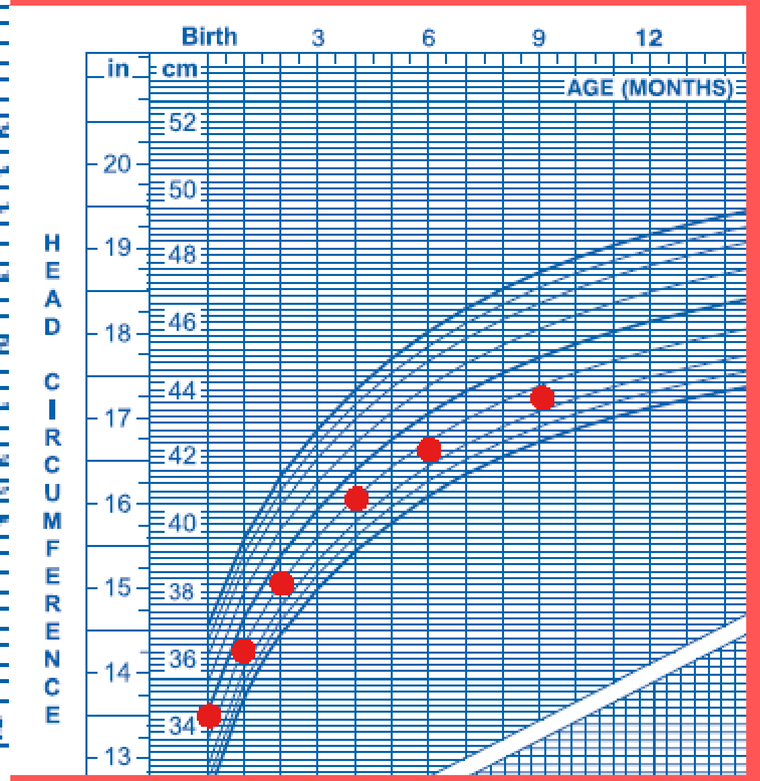
WT: 6.8 KG (<2ND%TILE)

HC: 44 CM (10-25TH%TILE)

BP 98/65

HR 82





Ready for Key Features?

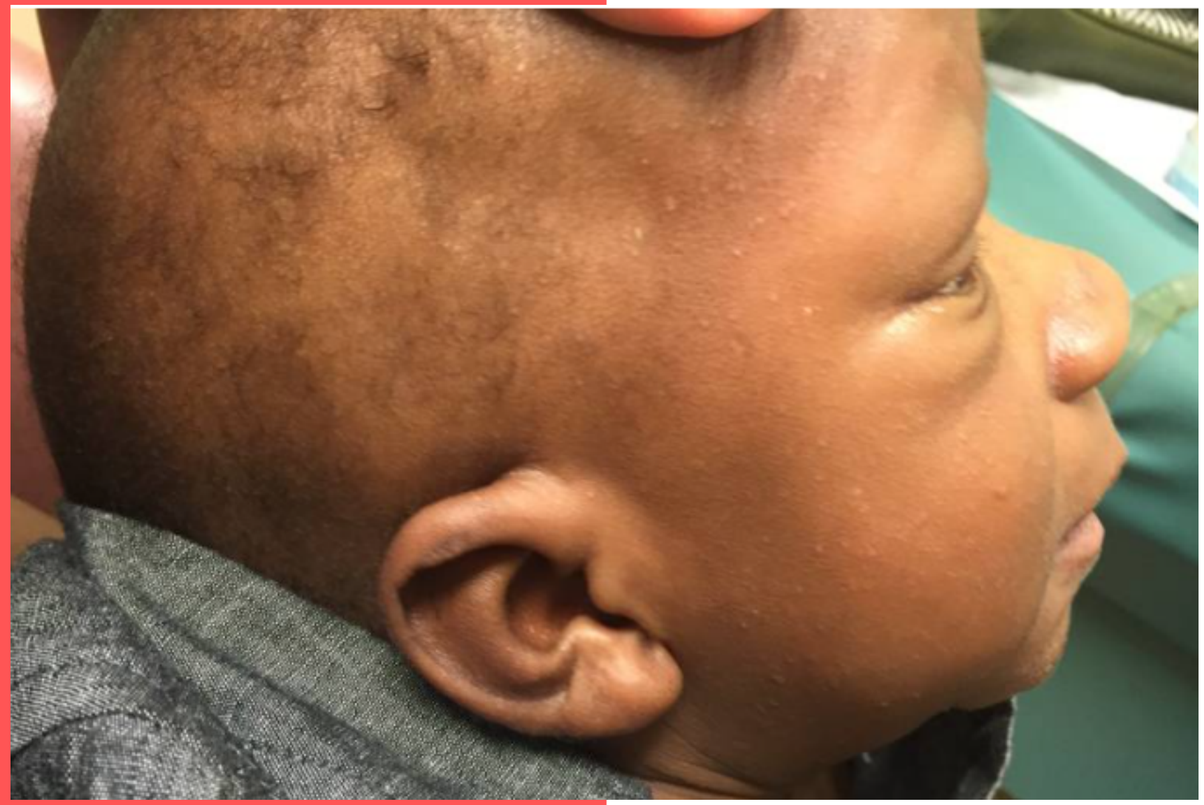
Time to check your general initial impression...

As you walk in, observe his head and face, his interactions, and his behaviors.

Although you perform a comprehensive exam on an undressed infant, we will not address all findings. If something is not mentioned, then it was normal.

Face

- tall forehead
- wide spaced eyes
- right ptosis
- down-slanting palpebral fissures
- depressed nasal bridge

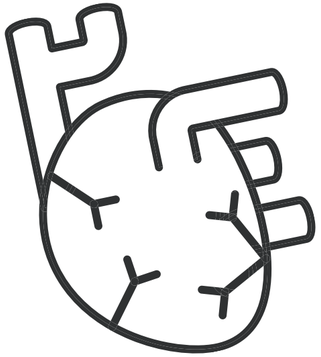


Head & Neck

- Low set, posteriorly rotated ears
- Thickened helix
- Short neck
- Not seen in this photo:
  - webbed neck
  - low posterior hairline

Chest

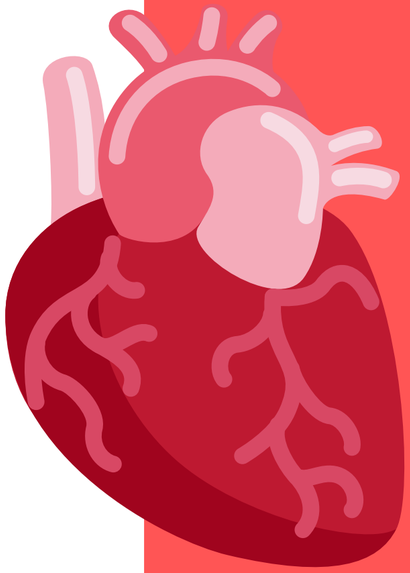
- sternotomy scar
- wide spaced nipples



Heart

*The mother pulls a report from her purse, it's an echo. The following were noted in the impression....

- septal hypertrophy
- severe pulmonary valve stenosis
- atrial septal defect

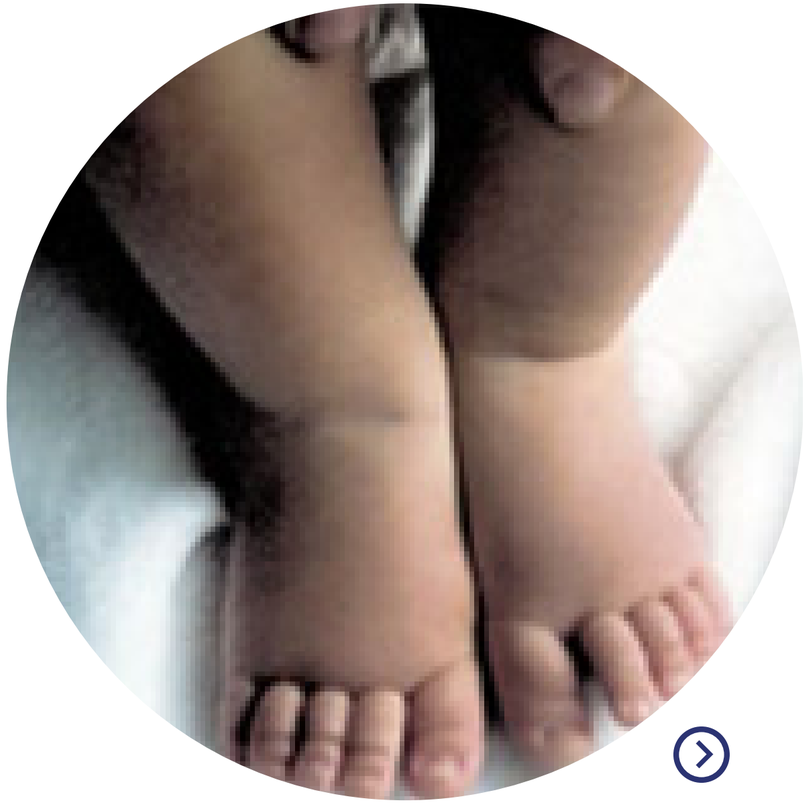


Diaper Check

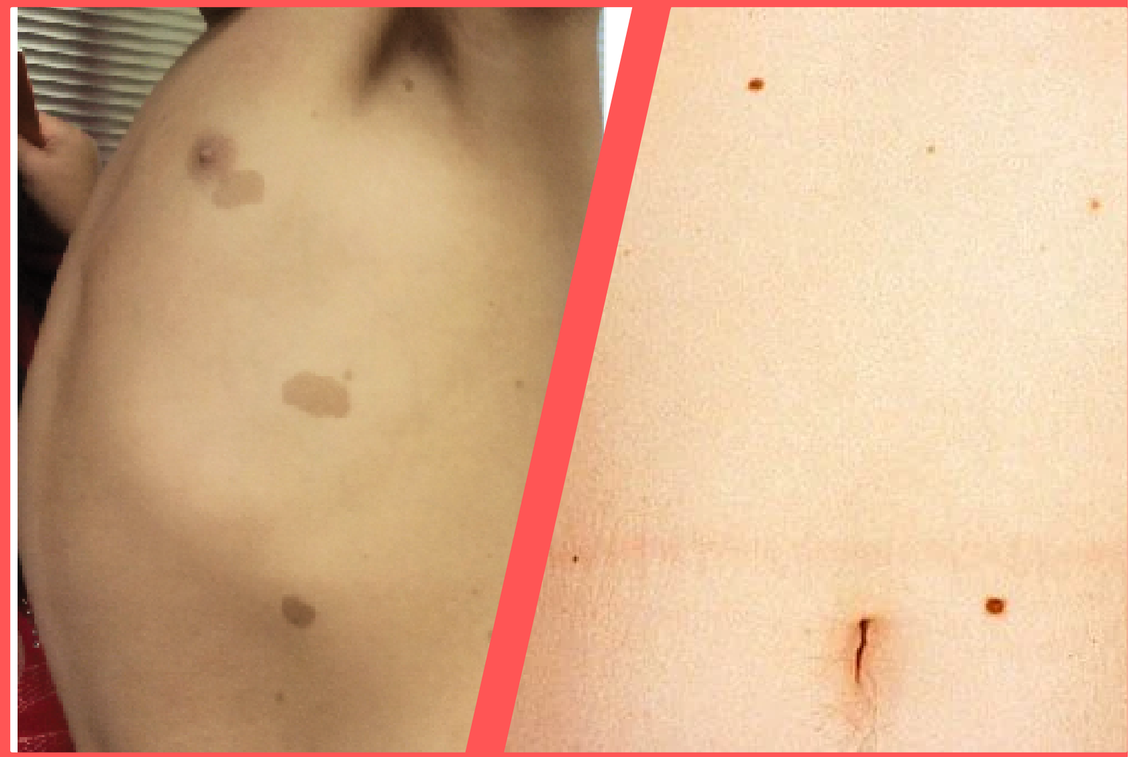
- cryptorchidism
- small penis

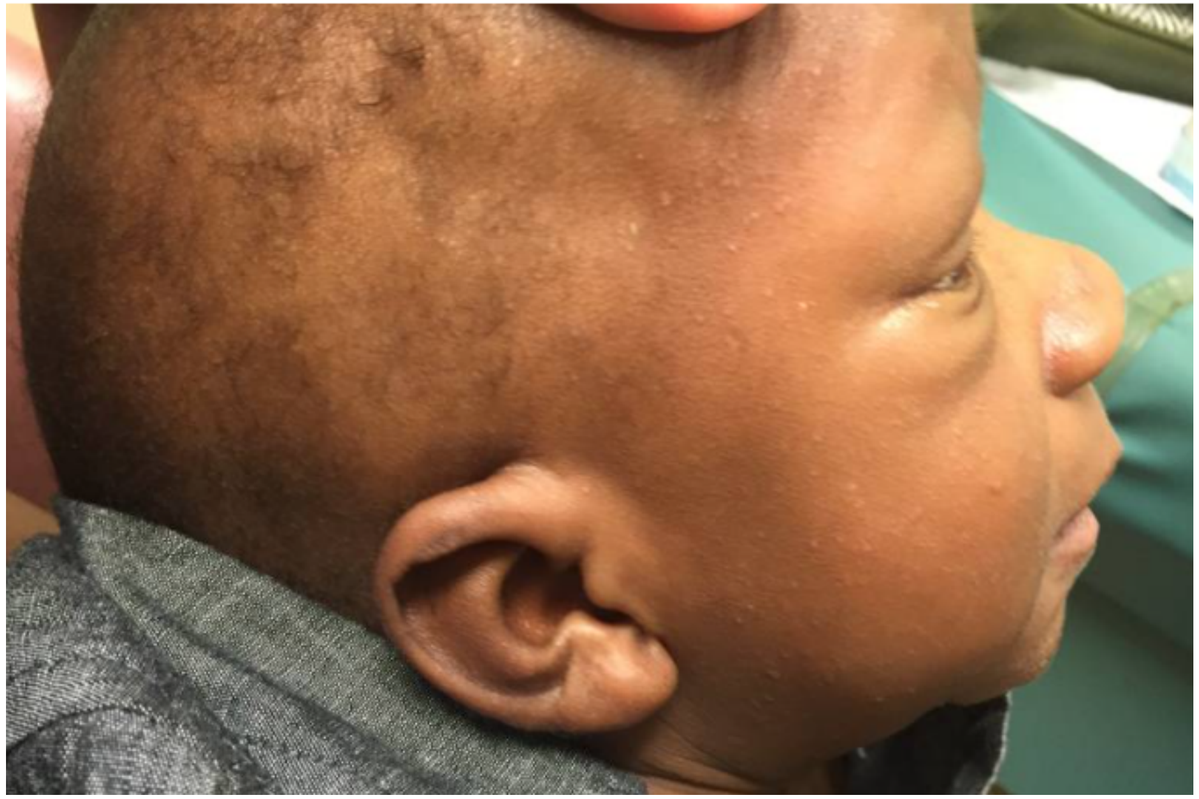
Musculoskeletal and neurologic exam

Head lag, lax joints, wearing SMOs, feet look a little puffy



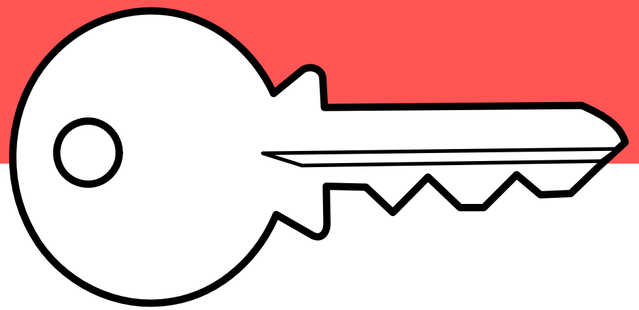
Skin





- Cafe au lait macules
- Multiple nevi
- Sparse hair

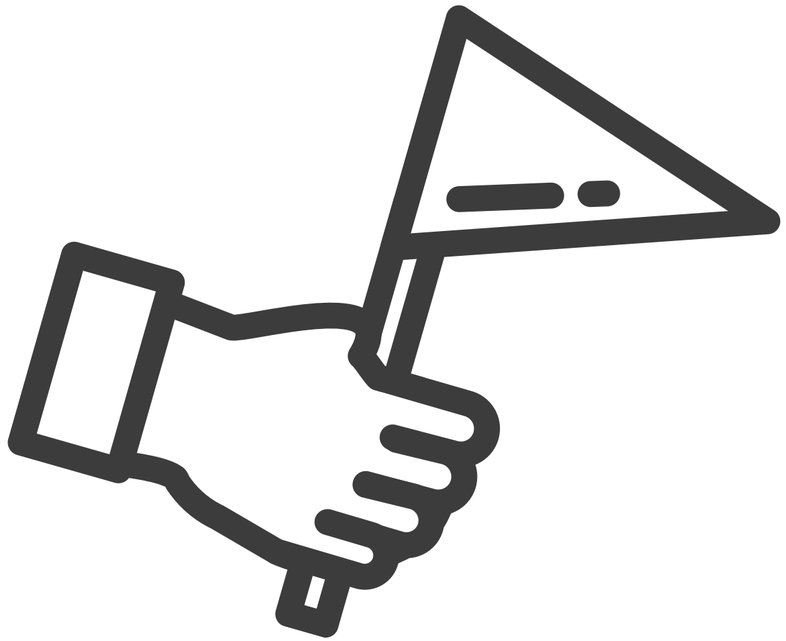
15 Minutes are up...



- short stature
- underweight
- relatively large head
- dysmorphic facial features
- short, webbed neck
- wide-spaced nipples and repaired congenital heart disease
- undescended testicles
- low muscle tone with delayed development
- mother with learning disability and similar facial features

Assessment and Plan

1. Encounter for routine child health examination with abnormal findings
    a. Anticipatory guidance
    b. Immunizations
2. Lack of growth
    a. Screening labs: CBC, TSH/FT4, CMP, IGF-1, IGFBP3
3. Global developmental delays
    a. Early Childhood intervention, continue private therapies
4. Ptosis
    a. Ophthalmology referral
5. Cryptorchidism
    a. Surgery or Urology referral
6. Dysmorphic features
    a. Genetics referral
7. Repaired congenital heart disease
    a. Continue care with cardiology



Genetics Referral completed

- Genetic testing was ordered and completed
- The following was tested: BRAF, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1
- A positive DNA mutation was found in the PTPN11 gene
    - Mother has the same mutation
- Clinical and molecular diagnosis of Noonan syndrome
- Genetic counseling on autosomal dominant inheritance
- Surveillance and therapies were recommended according to published guidelines

Did you make it to lunch?

The challenge for each well visit is to identify potential red flags that need further evaluation and possibly intervention

You don't need to make a specific genetic diagnosis but recognize when things are not as expected

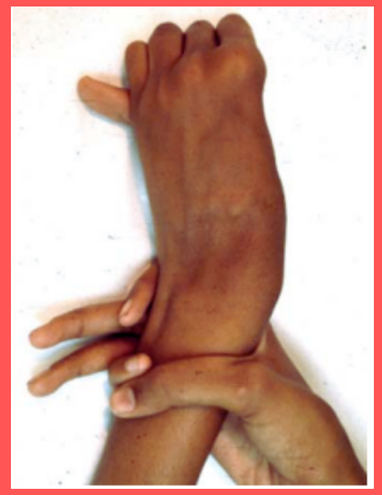
The Rule of Too/Two

- This rule was created by Dr. Grix
  - Genetics in Primary Care Institute, a project supported by the Maternal and Child Health Bureau, 2011-14.

- Use to quickly screen patients for genetic red flags

Rule of Too/Two

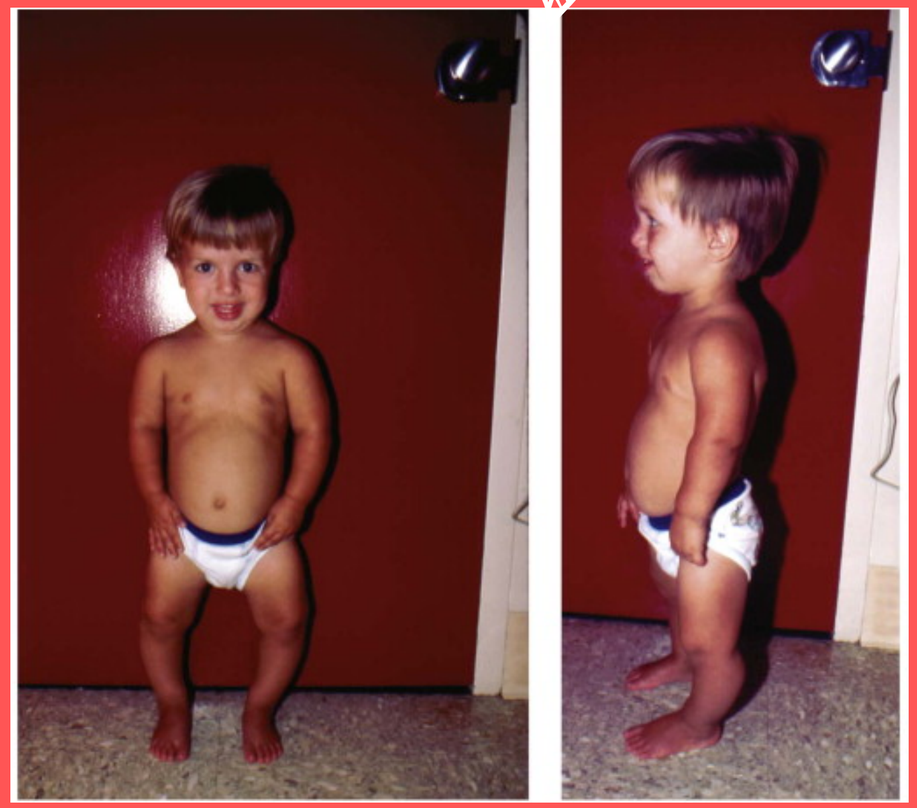
- Too tall
- Too small
- Too early
- Too many
- Too different
- Two tumors
- Two generations
- Two in the family
- Two birth defects

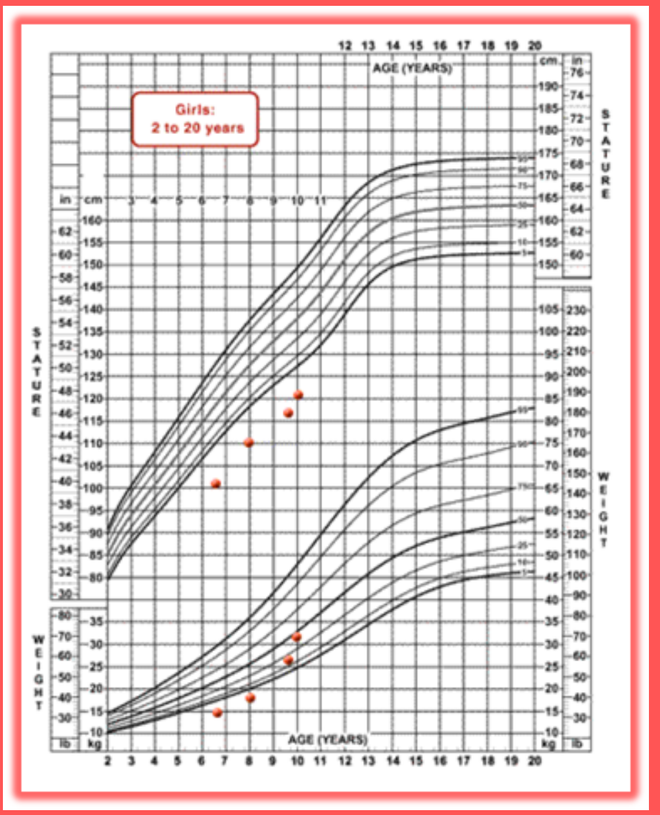


TOO TALL

HEIGHT ABOVE 97TH PERCENTILE FOR AGE AND SEX

MORE THAN 2SD ABOVE THE MEAN





TOO SMALL

HEIGHT BELOW 2ND PERCENTILE FOR AGE AND SEX

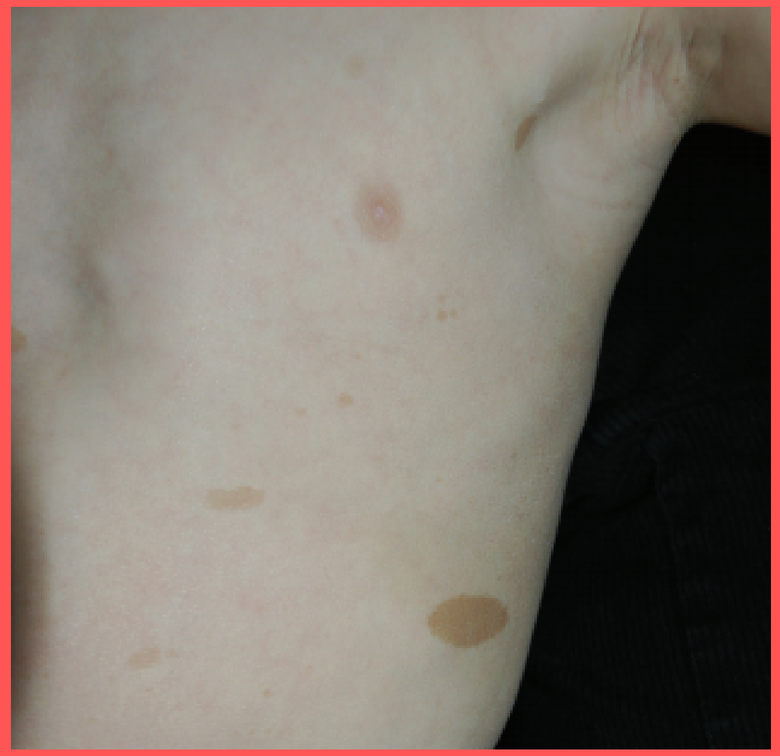
LESS THAN 2SD BELOW THE MEAN

TOO EARLY

- **CEREBRAL VASCULAR ACCIDENT IN ADOLESCENT**
- CONGENITAL **SENSORINEURAL HEARING LOSS**
- **LOSS OF VISION BY 20 YEARS**
- **FAMILY HISTORY OF SUDDEN DEATH**
- **FAMILY HISTORY OF CANCER BEFORE THE AGE OF 50 YEARS**

Too many

Almost anytime there is more than 6 of something....



Too many fractures, too many specialists, too many infections, etc.

01

CREATINE KINASE

One of the most powerful things you can order for a child that toe walks, has elevated liver enzymes, and HYPOTONIA is a CK. An elvated CK is ALWAYS a red flag for genetics.

TOO DIFFERENT

- ABNORMAL LABS IN AN OTHERWISE HEALTHY CHILD, E.G. ELEVATED LDL CHOLESTEROL
- ABNORMAL NEWBORN SCREEN
- GLOBAL DEVELOPMENTAL DELAY
- INTELLECTUAL DISABILITY
- HEAD IS TOO SMALL(< 2 SD, <2%)
- HEAD IS TOO BIG (>2 SD, >98%)
- TOE WALKING, ESPECIALLY IN MALE WITH LARGE CALVES
- SKIN IS TOO STRETCHY, THIN, OR SCARRED
- NO HAIR OR TEETH

TWO TUMORS

Two primary sites

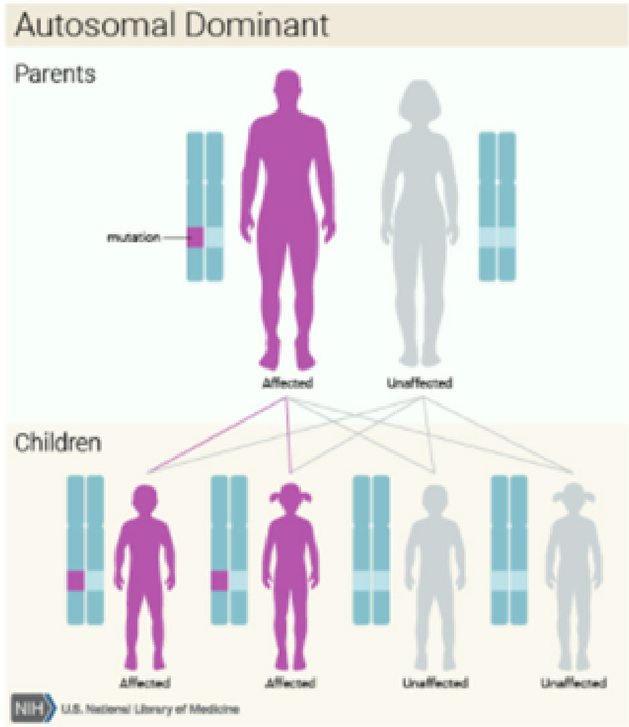
1. Bilateral breast cancer
2. Bilateral retinoblastoma
3. Bilateral schwannomas

Two types of tumors in the same person

1. Breast and ovarian cancer
2. Medullary thyroid carcinoma and pheochromocytoma
3. Follicular thyroid cancer and breast cancer

TWO Generations

Examples would include: Marfan syndrome, Noonan syndrome, 22q11 deletion syndrome, Neurofibromatosis type 1, Huntington syndrome, autosomal dominant polycystic kidney disease



U.S. National Library of Medicine

Family History

What families report and what a geneticist suspects

Father HTN
Paternal uncle HTN, dialysis
Paternal grandmother kidney transplant

Autosomal dominant kidney disease
*Check patient's blood pressure
*Ask more questions about age of onset, and if there's a known diagnosis

Family History

What families report and what a geneticist suspects

Mother arrhythmia
Maternal aunt deceased, drowning
Maternal grandfather arrhythmia

Autosomal dominant Long QT syndrome
*Check patient's ECG
*Ask more questions about age of onset, and if there's a known diagnosis

Family History

What families report and what a geneticist suspects

Mother tall, history of thyroid cancer
Sister autism, large head
Maternal uncle tall, autism
Maternal grandmother benign breast disease, history of thyroid cancer

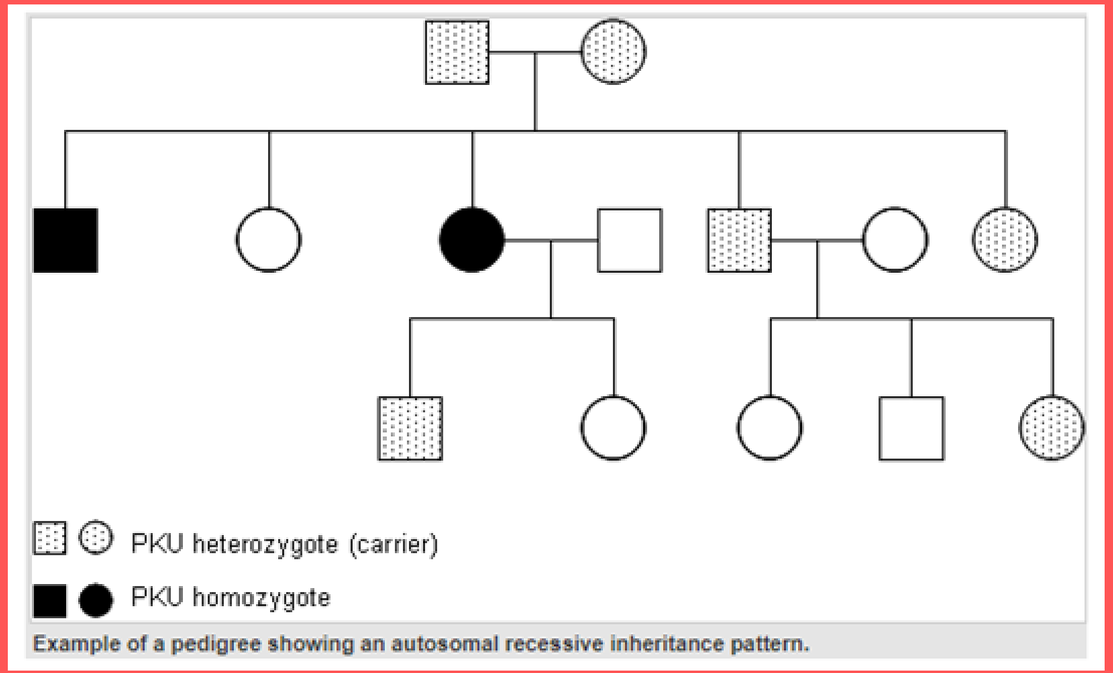
→

Autosomal dominant PTEN-related syndrome
*Check patient's head size
*Measure mother's head
*Review developmental milestones
*Ask more questions about age of onset, and if there's a known diagnosis

→

TWO IN THE FAMILY

2 or more siblings affected with same disorder, e.g. spinal muscular atrophy, PKU, cystic fibrosis, autism



Example of a pedigree showing an autosomal recessive inheritance pattern.

TWO BIRTH DEFECTS

Congenital anomalies denote a wide range of abnormalities of body structure or function that are present at birth and are of prenatal origin

Major = structural changes that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention.

Minor = structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual.

Major Anomalies

3% of newborns have a major defect

Major anomalies recognized in 5-7% between 2-5 years

Box 1.1. Selected major congenital anomalies

External	Internal

• Neural tube defects
  ◦ Anencephaly
  ◦ Craniorachischisis
  ◦ Iniencephaly
  ◦ Encephalocele
  ◦ Spina bifida
• Microcephaly
• Microtia/Anotia
• Orofacial clefts
  ◦ Cleft lip only
  ◦ Cleft palate only
  ◦ Cleft lip and palate
• Exomphalos (omphalocele)
• Gastroschisis
• Hypospadias
• Reduction defects of upper and lower limbs
• Talipes equinovarus/club foot
	• Congenital heart defects
	  ◦ Hypoplastic left heart syndrome
	  ◦ Common truncus
	  ◦ Interrupted aortic arch
	  ◦ Transposition of great arteries
	  ◦ Tetralogy of Fallot
	  ◦ Pulmonary valve atresia
	  ◦ Tricuspid valve atresia
	• Esophageal atresia/tracheoesophageal fistula
	• Large intestinal atresia/stenosis
	• Anorectal atresia/stenosis
	• Renal agenesis/hypoplasia

Minor Anomalies

- 15% of newborns will have a single minor anomaly
- 0.8% of newborns will have two minor anomalies
- 0.5% will have three minor anomalies
- 20% of newborns with 3 or more minor anomalies have a major anomaly and/or syndrome
- 4o% of children with DD/ID have 3 or more minor anomalies

Box 1.2. Selected external minor congenital anomalies

Absent nails	Lop ear
Accessory tragus	Micrognathia
Anterior anus (ectopic anus)	Natal teeth
Auricular tag or pit	Overlapping digits
Bifid uvula or cleft uvula	Plagiocephaly
Branchial tag or pit	Polydactyly type B tag, involves hand and foot
Camptodactyly	Preauricular appendage, tag or lobule
Cup ear	Redundant neck folds
Cutis aplasia (if large, this is a major anomaly)	Rocker-bottom feet
Ear lobe crease	Single crease, fifth finger
Ear lobe notch	Single transverse palmar crease
Ear pit or tag	Single umbilical artery
Extra nipples (supernumerary nipples)	Small penis (unless documented as micropenis)
Facial asymmetry	Syndactyly involving second and third toes
Hydrocele	Tongue-tie (ankyloglossia)
Hypoplastic fingernails	Umbilical hernia
Hypoplastic toenails	Undescended testicle
Iris coloboma	Webbed neck (pterygium colli)

Rule of Too/Two

- Too tall
- Too small
- Too early
- Too many
- Too different
- Two tumors
- Two generations
- Two in the family
- Two birth defects

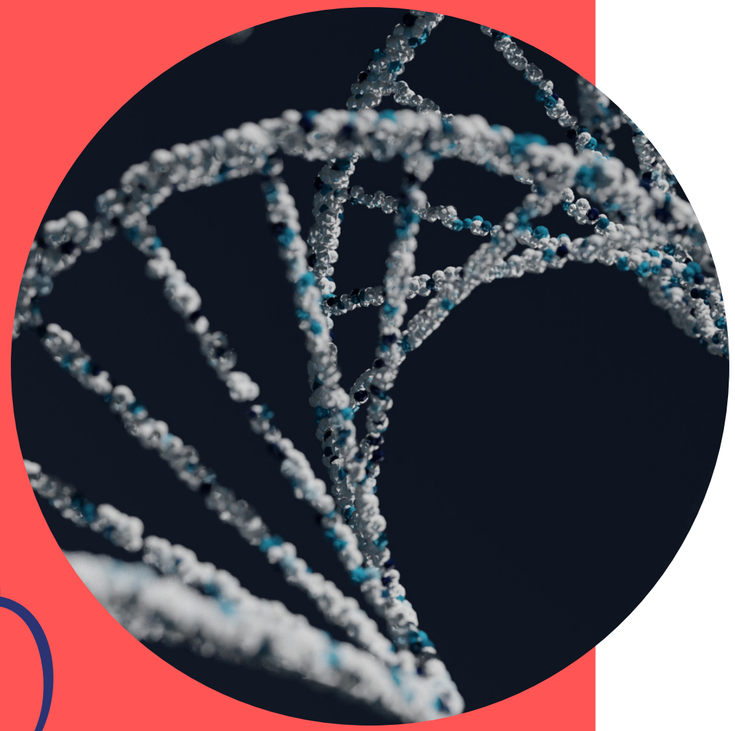
June 2007 • Vol. 9 • No. 6

ACMG Practice Guideline

Indications for genetic referral: a guide for healthcare providers

Beth A. Pletcher, MD[1], Helga V. Toriello, PhD[2], Sarah J. Noblin, MS, CGC[3], Laurie H. Seaver, MD[4], Deborah A. Driscoll, MD[5], Robin L. Bennett, MS[6], and Susan J. Gross, MD[7]

- Congenital hypotonia or hypertonia
- Unexplained intrauterine growth retardation
- A single major, or multiple major and/or minor anomalies
- Dysmorphic features that are not familial, especially accompanied by developmental delays or intellectual disability
- Abnormal brain MRI findings such as leukodystrophy, periventricular calcifications, unidentified bright objects, or a malformation
- An **abnormal newborn screening** test
- A known **metabolic disorder** or symptoms of a metabolic disorder such as intractable seizures, hepatosplenomegaly, acidosis, cyclic vomiting, persistent hypoglycemia, developmental regression, and unusual body odor
- Evidence of a **connective tissue disorder** such as extreme joint laxity, poor wound healing, or a marfanoid habitus
- **Failure to thrive**
- A **significant family history** of a medical or psychiatric conditions that puts the patient at risk of developing the same or similar condition
- Born to a parent with a **known chromosomal abnormality** or rearrangement
- A **recognized or suspected genetic syndrome** including a chromosomal or single gene disorder
- **Congenital eye defects** or blindness associated with problems such as microophthalmia, cataracts, megalocornea, retinitis pigmentosa, or cone-rod dystrophy
- 6 or more **café-au-lait** macules >0.5 cm in diameter
- Unusual **skin findings** such as a multiple types of lesions, multiple lipomas, numerous hypo- or hyperpigmented lesions, and albinism
- **Significant hearing loss** or deafness not secondary to recurrent otitis media
- An **unusual growth pattern** such as overgrowth, short stature, or hemihypertrophy
- Unexplained **intellectual disability** or global **developmental delay**
- **Autism** or pervasive developmental disorder
- **Unusual behaviors**, especially when associated with minor malformations and developmental delays or ID
- **Bilateral or multifocal malignancies** such a retinoblastoma or Wilms tumor
- Problems with **clotting** including disorders such as hemophilia and thrombophilia
- An **immunodeficiency** or significant immune problem
- **Progressive muscle weakness** or other neurologic conditions that might be associated with a genetic disorder
- **Cardiomyopathy** not secondary to a viral infection



Summary

- Well visits are opportunities to identify red flags
- Red flags indicate a need for further evaluation
- Multiples in a patient's history, patient's exam, and/or patient's family history is a significant flag for genetic referral
- If a genetic referral will take months to complete, reach out to your referral clinic and ask about possible evaluations while waiting

Resources

- www.mountainstatesgenetics.org/for-professionals/for-primary-care-clinicians/
- www.acmg.net
  - https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508
- National Society of Genetic Counselors (nsgc.org)
- Rare Disease Information - NORD (National Organization for Rare Disorders) (rarediseases.org)
- Online Mendelian Inheritance in Man (omim.org)
- Gene Reviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/)
- Formerly Genetic Home Reference (https://medlineplus.gov/genetics/)
- Council on Genetics | American Academy of Pediatrics (aappublications.org)
- https://www.jax.org/education-and-learning/clinical-and-continuing-education/precision-medicine-for-your-practice

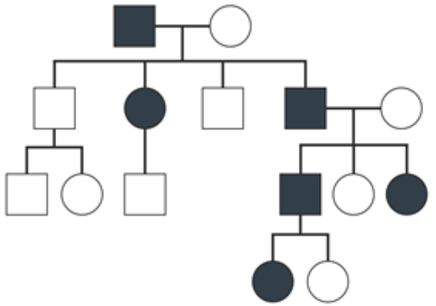
Nailed it

References and Credits

- Whelan AJ, Ball S, Best L, et al. Genetic red flags: clues to thinking genetically in primary care practice. Prim Care. 2004;31(3):497-508
- Noonan syndrome - Atlas of Human Malformation Syndromes in Diverse Populations (nih.gov)
- Credit:Courtesy of Sam Butler,https://www.pri.org/stories/2020-07-24/special-friends-dolls-reflect-lives-children-special-needs
- https://cfvod.kaltura.com/p/816122/sp/81612200/thumbnail/entry_id/0_fvy9a0g3/version/100012/width/640
- https://surestep.net/wp-content/uploads/2017/04/SMo-4.jpg
- https://tss.org.uk/images/stories/handandfeet.jpg
- https://www.ctf.org/images/uploads/documents/PossibleNF1_CafeAuLaitSpots_(1).pdf
- Genetics in Primary Care Initiative, Toolkit, 2014
- https://www.mayoclinic.org/diseases-conditions/marfan-syndrome/symptoms-causes/syc-20350782

References and Credits

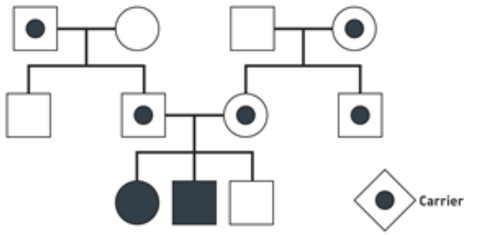
- Shirley ED, Sponseller PD. Marfan syndrome. J Am Acad Orthop Surg. 2009 Sep;17(9):572-81. doi: 10.5435/00124635-200909000-00004. PMID: 19726741.
- Jones, Kenneth, Marilyn Jones, and Miguel Campo. Smith's Recognizable Patterns of Human Malformation. 7th ed. Elsevier Health Sciences, 2013.
- https://www.magicfoundation.org/Growth-Disorders/Russell-Silver-Syndrome/
- http://depts.washington.edu/growth/cshcn/text/page5b.htm
- Kapoor R, Johnson RA. Images in clinical medicine. Polydactyly. N Engl J Med. 2011 Dec 1;365(22):2122. doi: 10.1056/NEJMicm1100857. PMID: 22129256.
- https://medlineplus.gov/genetics/understanding/inheritance/inheritancepatterns/
- https://www.nature.com/scitable/content/example-of-a-pedigree-showing-an-autosomal-6618
- https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html



Autosomal Dominant Inheritance

- Individuals affected in every generation
- Some carriers may not manifest disease
- Males and females have equal chance of passing on mutation
- 50% risk to children

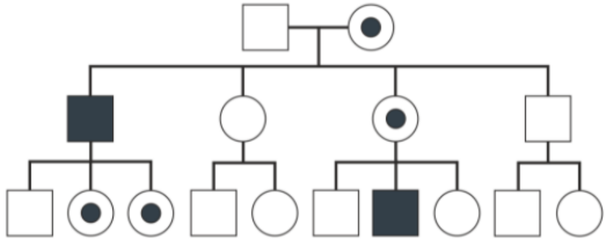
https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/inheritance-patterns



Autosomal Recessive Inheritance

- May be only one generation affected
- Carriers typically do not have condition
- Both parents must be carriers of the mutation
- 25% risk to children

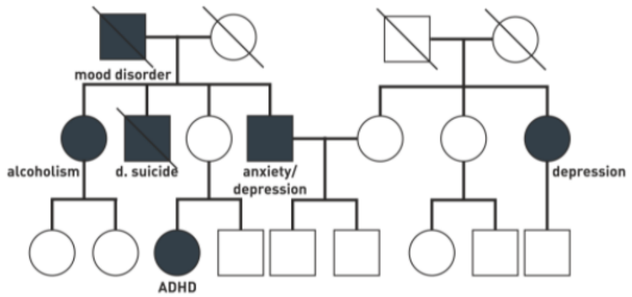
https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/inheritance-patterns



X-linked Inheritance

- No male-to-male transmission
- Though rare, females can be affected if they inherited two mutations
- Many female carriers (one mutation) will have no symptoms; those that do have milder symptoms than seen in males
- Risk for inheriting an X-linked condition:
  - 100% for daughters of affected fathers to be carriers
  - 0% for sons of affected fathers to be affected
  - 50% for daughters of carrier or affected mothers to be carriers
  - 100% for sons of affected mothers to be affected
  - 50% for sons of carrier mothers to be affected

https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/inheritance-patterns



Complex Inheritance

- No clear Mendelian pattern of inheritance
- Clustering of biologically related conditions in the family
- Risk estimates based primarily on empiric data
- The chance of developing a complex trait depends on several factors, which may include:
  - The number of relatives affected with a condition (or related conditions)
  - How closely one is related to the affected individual(s)
  - Similarity of the shared environment and lifestyle factors
  - Severity of the condition in the affected relative
  - The age at onset in the affected family member
  - The sex of the affected family member
  - Ethnicity

https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/inheritance-patterns