Approach to Family History and Pedigrees – Part I

Developed by Erinna McMurtry and Jovana Miladinovic
Supervised by Dr. Patricia Blakley
University of Saskatchewan

peds cases | Pediatric Education Online

Learning objectives

1. Describe the utility of the family history based on clinical context.
2. Recognize common symbols and notations used to construct genetic pedigrees.
3. Draw an accurate genetic pedigree from a completed family history form.
4. Discuss the classic patterns of Mendelian inheritance (autosomal dominant, autosomal recessive, X-linked recessive and X-linked dominant inheritance) and recognize these patterns in a pedigree.*

* = covered in Approach to Pedigrees Part II

A case: Billy

History

Patient: Billy Martin, 9 year old boy

Chief complaint: “frequent sprained ankles and dragging feet”

History of presenting illness:

- frequent sprained ankles over the past couple months, increased tripping and falling
- change in gait ("dragging his feet")
- has always been "clumsy"

Past medical history:

- full-term infant with no prenatal or perinatal issues
- normal development, except for gross motor delay with concerns with his balance

Medications: None.

Physical exam

Vitals: BP 108/70, RR 19, HR 75. Height – 134cm, weight – 28.9kg.

Billy appeared well and alert. Pes cavus noted bilaterally but no other dysmorphic features seen.

Neurological exam: CN II-XII intact. Deep tendon reflexes normal, no clonus and negative Babinski sign. Good muscle bulk and tone, 5/5 strength bilaterally except ankle dorsiflexors which are 4/5 bilaterally. Normal sensation.

Gait was steady with foot drop noted.

What are our next steps for Billy?

1. Refer him to paediatric neurology for further testing.
2. Further history?

Why do we take family histories?

- Aid in the recognition of inherited susceptibilities, traits, and/or disorders, which can then inform:
  - Risk assessment
  - Relevant follow-up investigations
  - Preconception counseling
  - Preventative medicine
- Also a good tool for building rapport!
- Can foster a sense of responsibility and partnership in health management

Approach to taking a family history

- Comprehensive = health information about three generations of 1st, 2nd, and 3rd degree relatives
  - 1st degree relatives – share ~50% of genes – parents, full siblings
  - 2nd degree relatives – share ~25% of genes – half-siblings, uncles, aunts, grandparents
  - 3rd degree relatives – share ~12.5% of genes – first cousins
- Use the SCREEN mnemonic to remember some relevant questions:
  - SC – Some Concern
  - R – Reproduction
  - E – Early disease, death, or disability
  - E – Ethnicity
  - N – Non-genetic

Some **C**oncern	Do you have (some) any concerns about diseases or conditions that run in the family?
Reproduction	Have there been any problems with pregnancy, infertility, or birth defects in your family?
Early disease, death, disability	Have any members of your family died or become sick at an early age?
Ethnicity	How would you describe your ethnicity?
Non-genetic factors	Are there any other risk factors that run in your family?

Some **C**oncern	• Maternal grandfather has had some gait issues • Billy's mother (Sarah) has high arches (pes cavus) like Billy, and also has an unusual gait • Hemophilia runs in the family on Billy's father's side
Reproduction	• Maternal aunt has been unable to conceive • Sarah is currently pregnant
Early disease, death, disability	• Maternal grandfather developed gait disturbance in his 20s which has progressed; he uses a walker now • Paternal uncle was diagnosed with hemophilia B at young age
Ethnicity	• Maternal side = German • Paternal side = French
Non-genetic factors	• Paternal grandfather died of pancreatic cancer

Family history form

- See the attached document to review the completed family history form

Index Patient: Billy Martin Date of Birth January 18, 2013

Sex male Health Card # 123 456 789

Name of person completing this form Sarah Martin

Relationship to patient mother

Referring Doctor Dr. M

Family Doctor Dr. M

Reason for Referral gait issues that run in the family

Medical diagnosis if known

What questions do you have that you would like answered?

Can Billy be treated? Should I be worried about my pregnancy?

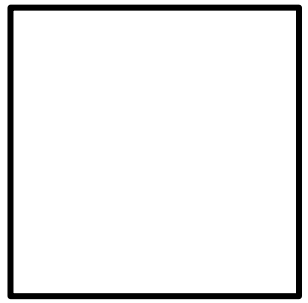
List any health problems the **INDEX PATIENT** has, or, if deceased, give the cause of death.

high arches, distal muscle wakness of both legs, abnormal gait

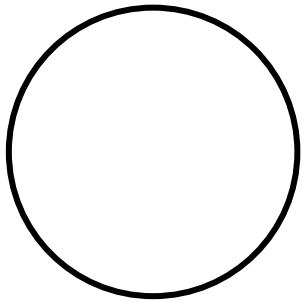
Intro to pedigrees

- We construct pedigrees because they help us determine:
  - if there is a genetic component contributing to a patient's presentation
  - if there are any patterns of traits or conditions present across generation
    - Which could be related to a genetic syndrome
- Helps us refine our differential and guide next steps
- It is important to use consistent and universal notation so that it is easily understood by other healthcare providers

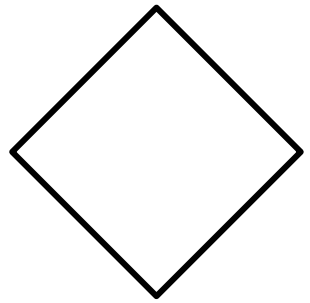
Basics



Unaffected
male

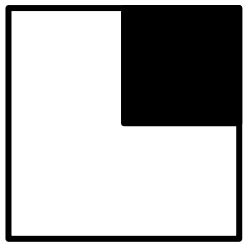


Unaffected
female

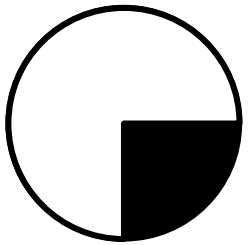


Unaffected
Sex unknown or
unspecified

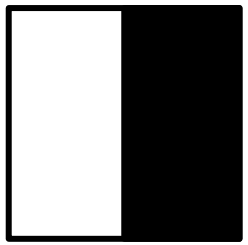
Indicating/marking/demonstrating specific traits



Male with blue eyes

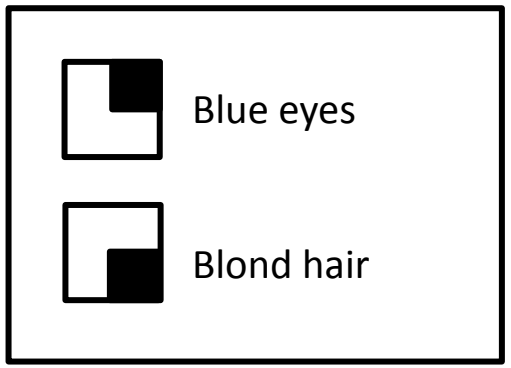


Female with blond hair

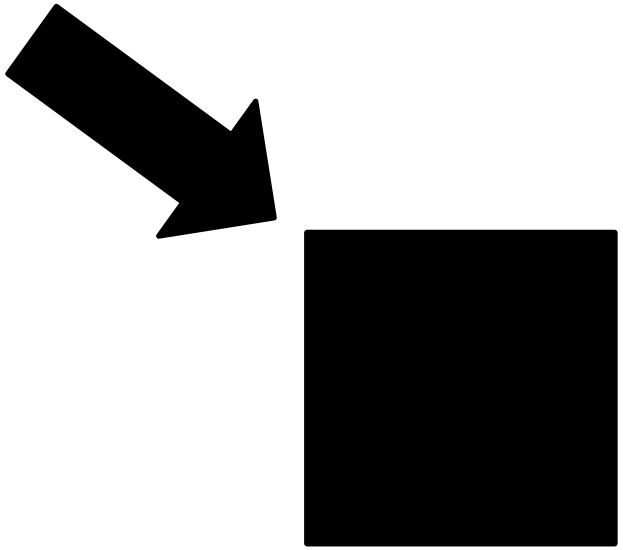


Male with blue eyes and blond hair

Legend

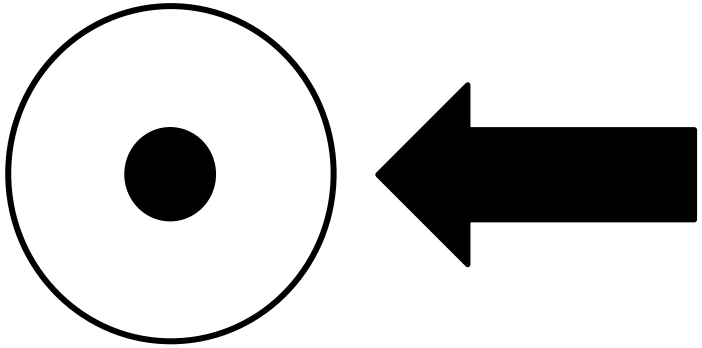


Index patient/proband



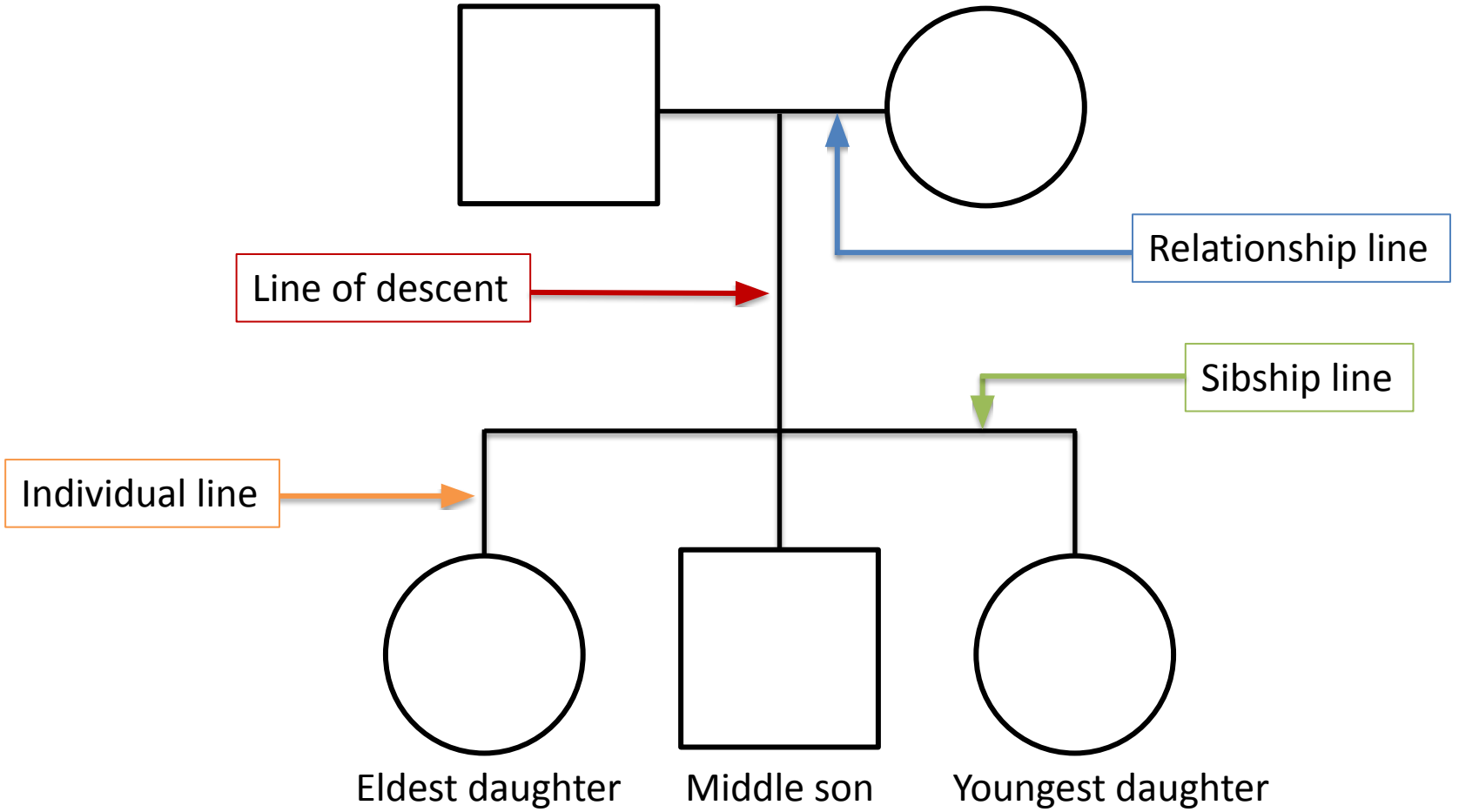
Jonathan B.
01/02/2003
Marfan syndrome dx 2007

Index patient/proband

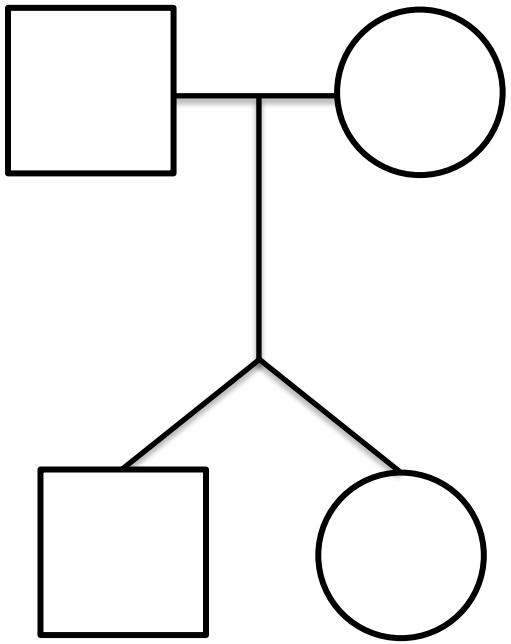


Maria T.
05/06/2007
Cystic fibrosis dx 2008

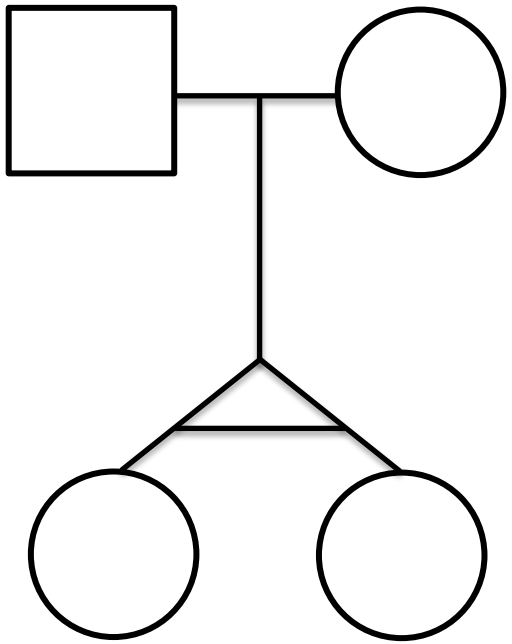
Lines


Relationship line
Line of descent
Sibship line
Individual line
Eldest daughter
Middle son
Youngest daughter

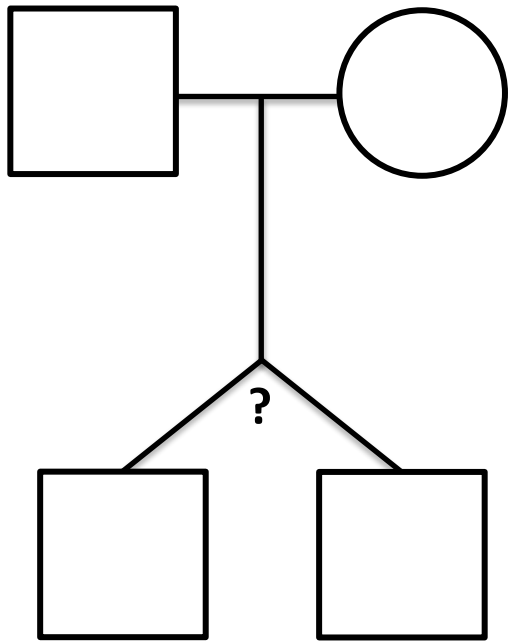
Twins



Dizygotic twins

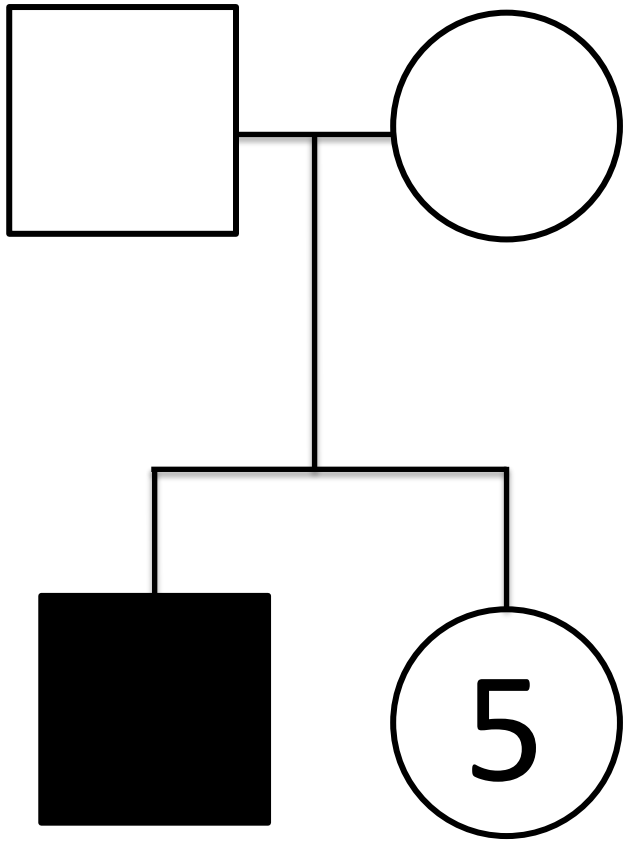


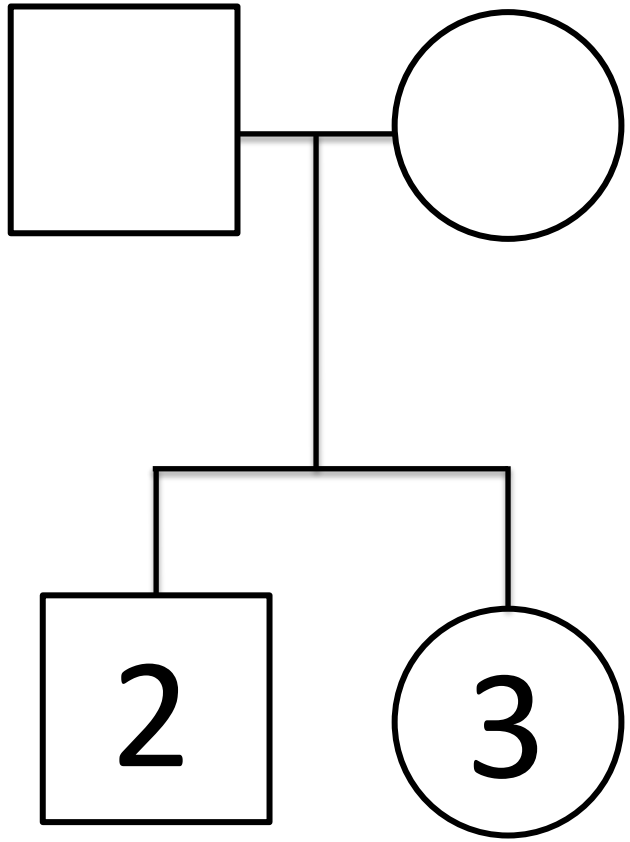
Monozygotic twins



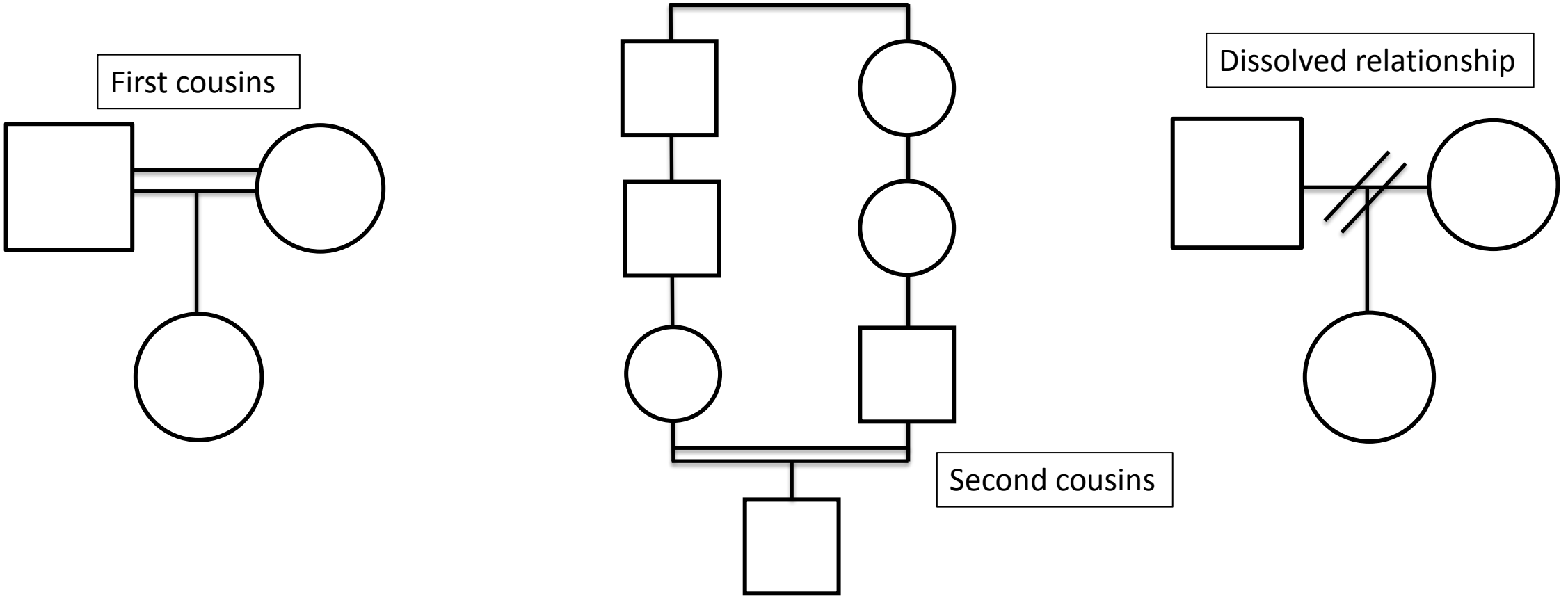
Unknown

Siblings – special cases

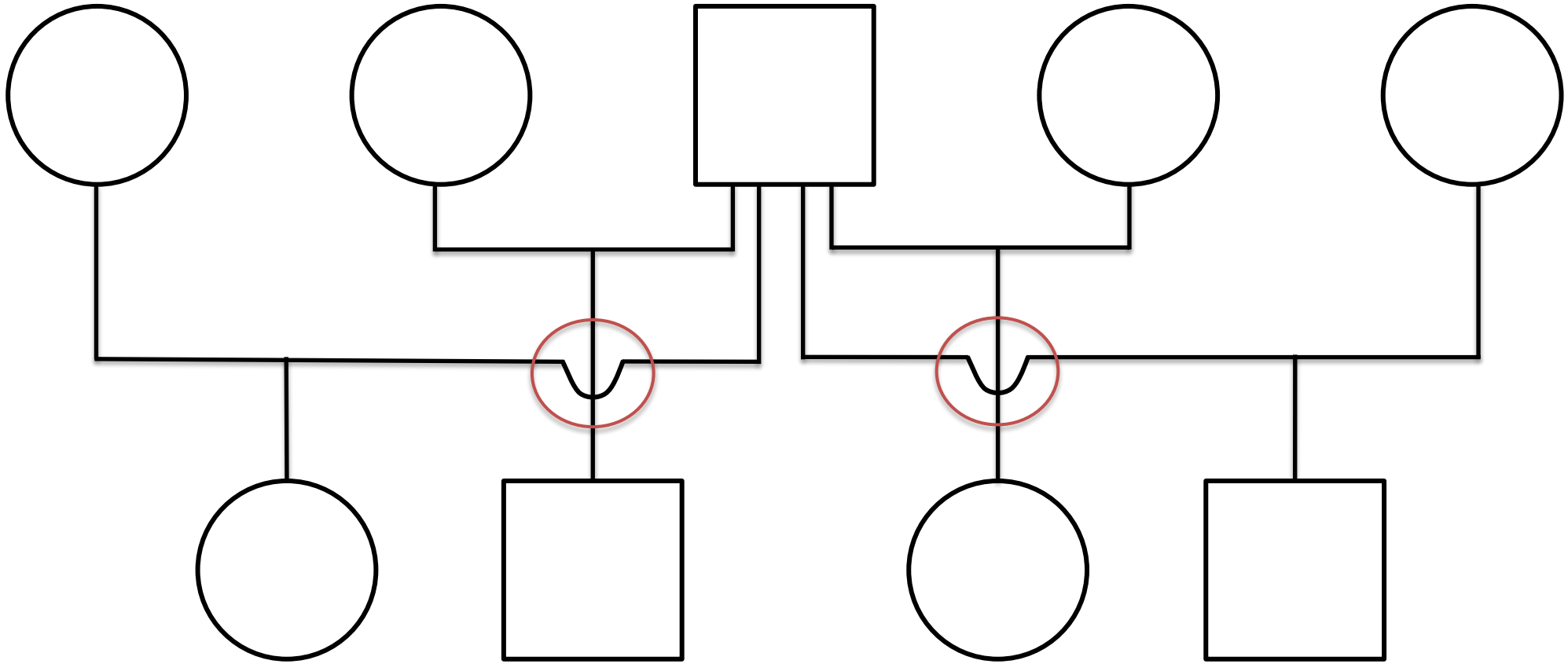




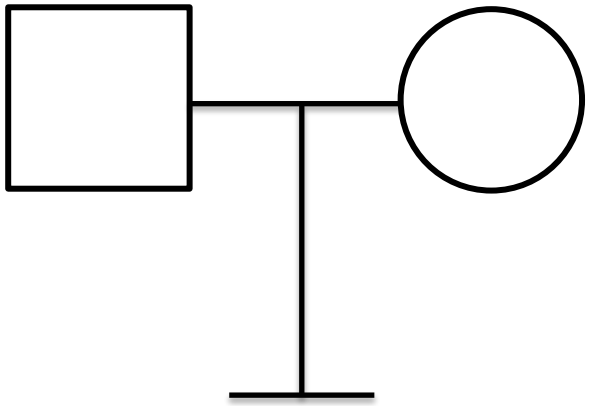
Consanguinity and dissolved relationships



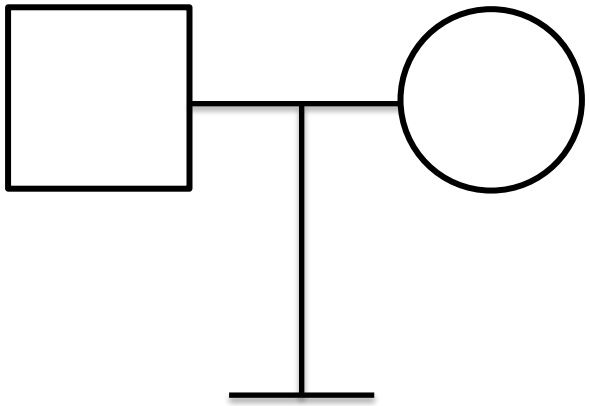
Overlapping lines



Couples with no children

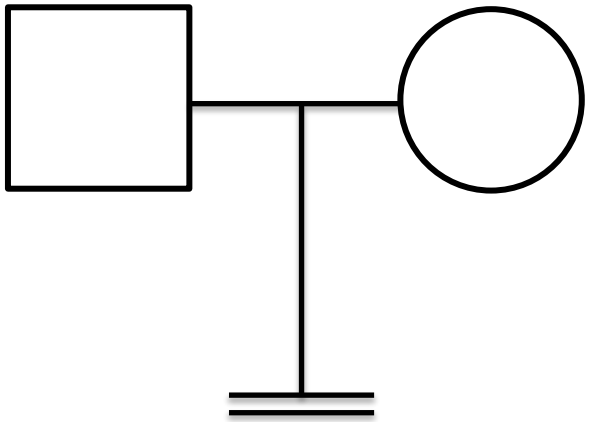


No children



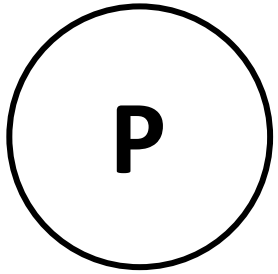
C

No children by choice

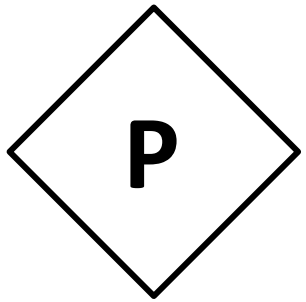


Infertility

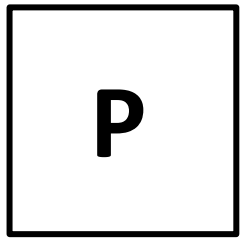
Pregnancy



EDC 12/12/2022



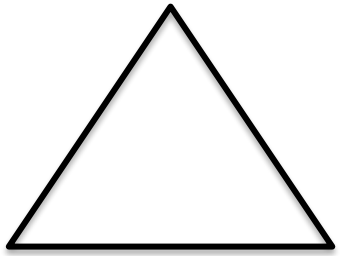
LMP 04/04/2022



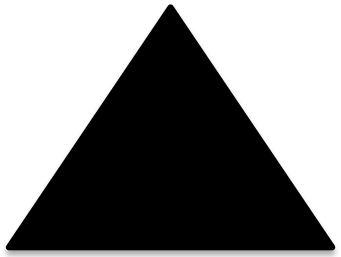
GA 20 weeks
47, XY, +21

LMP = last menstrual period
GA = gestational age
EDC = estimated date of confinement i.e. due date

Pregnancies not carried to term

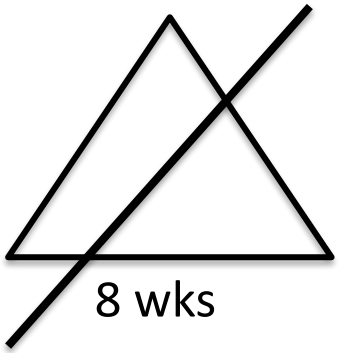


10 wks

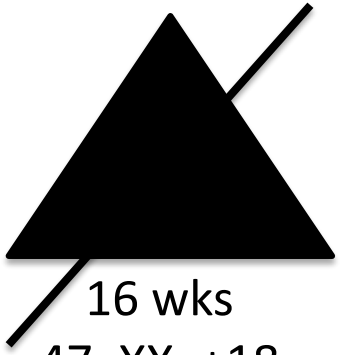


13 wks
47, XY, +16

Spontaneous abortion

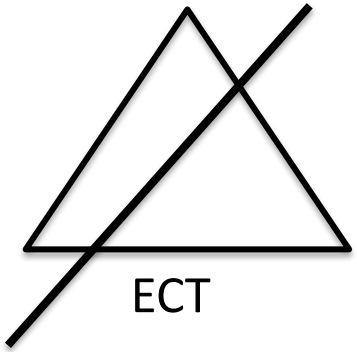


8 wks



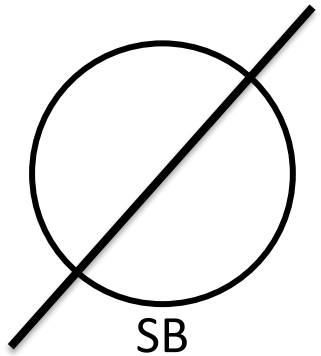
16 wks
47, XX, +18

Termination of pregnancy

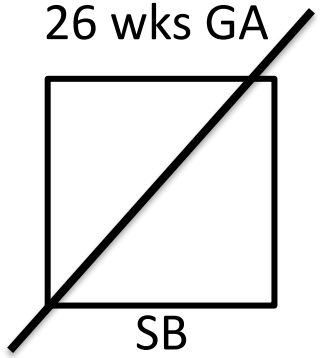


ECT

Ectopic pregnancy



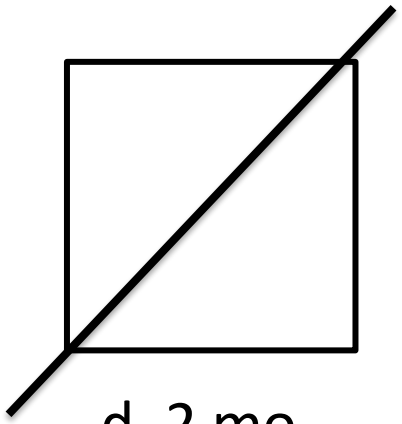
SB
26 wks GA



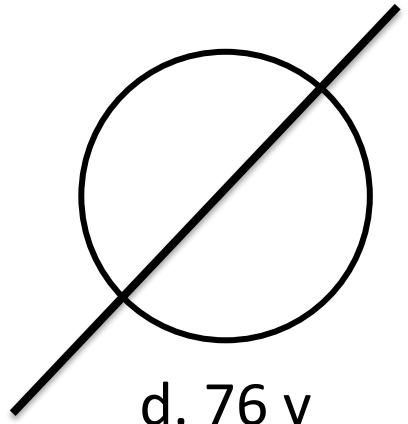
SB
21 wks GA

Stillbirth

Deceased individuals

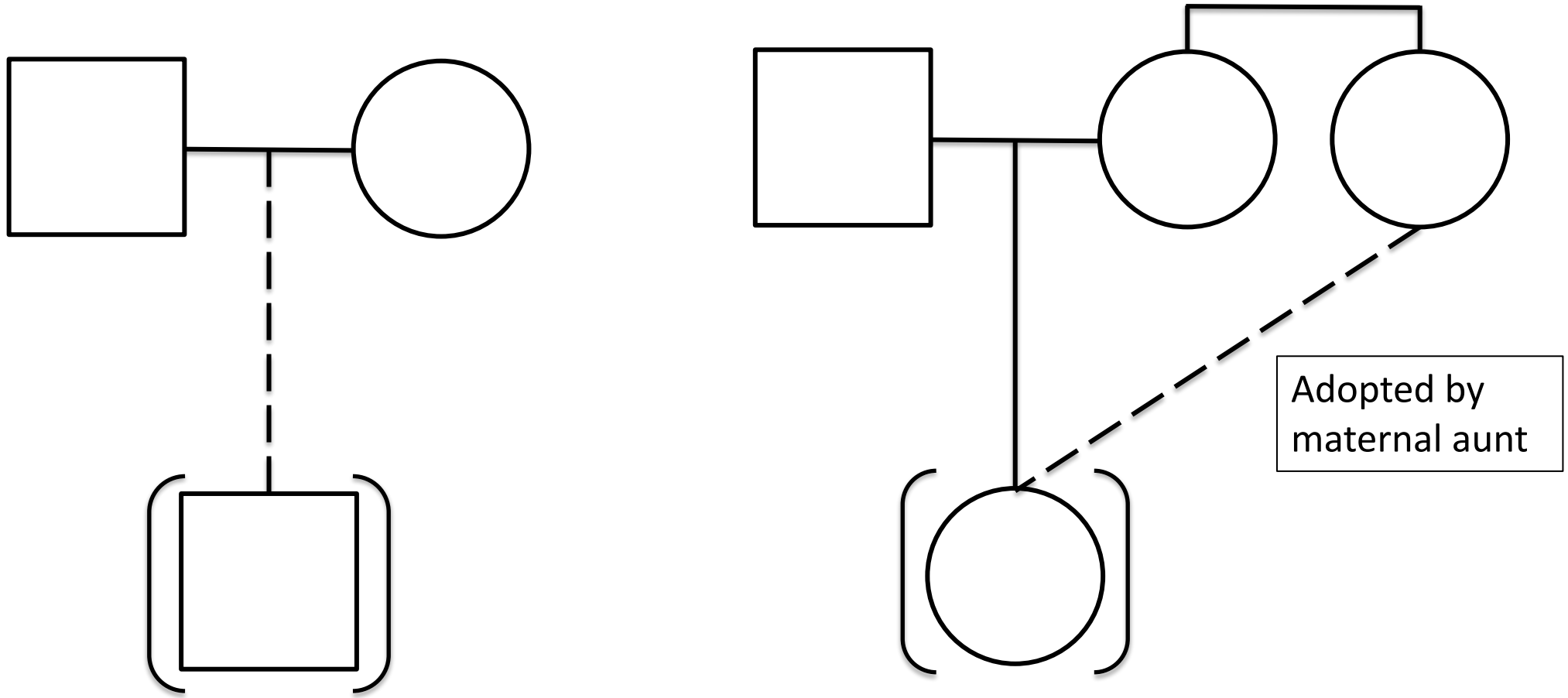


d. 2 mo.
SIDS



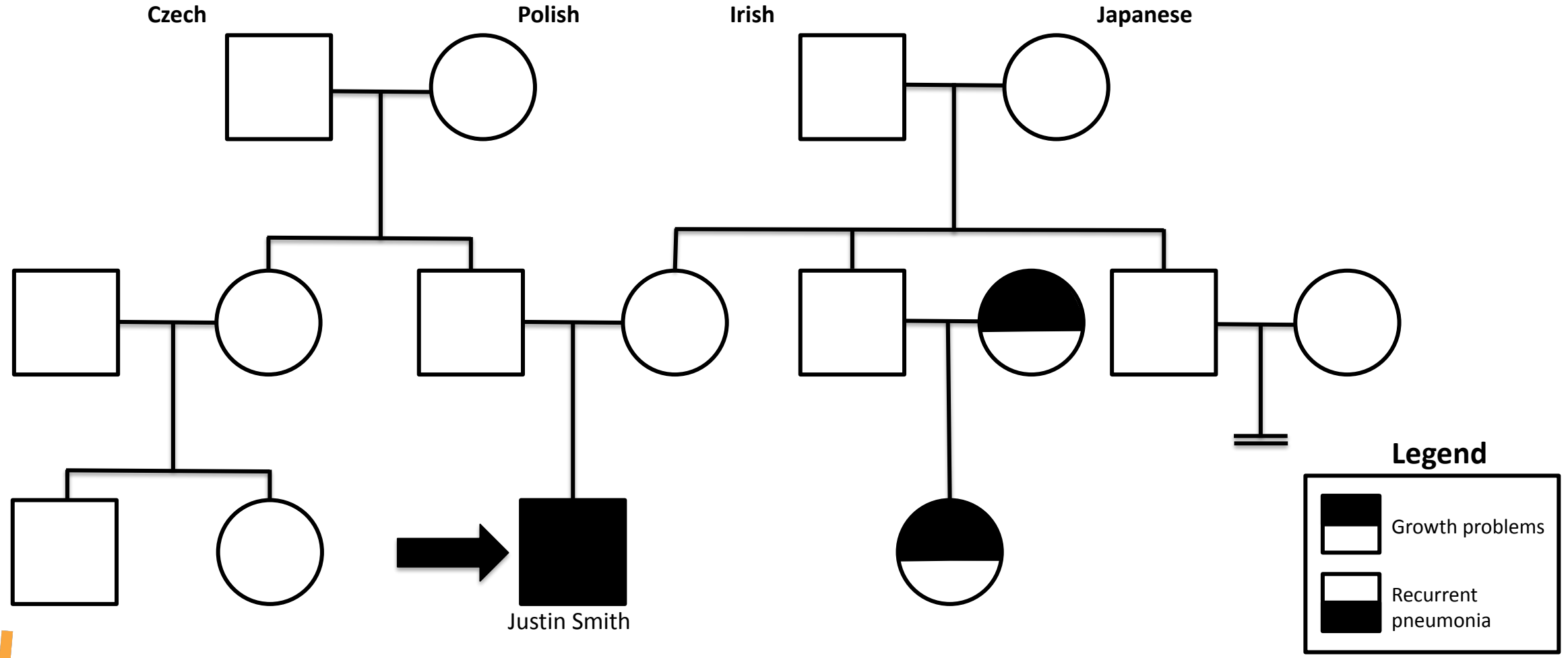
d. 76 y
Pancreatic cancer

Adoption



Additional features

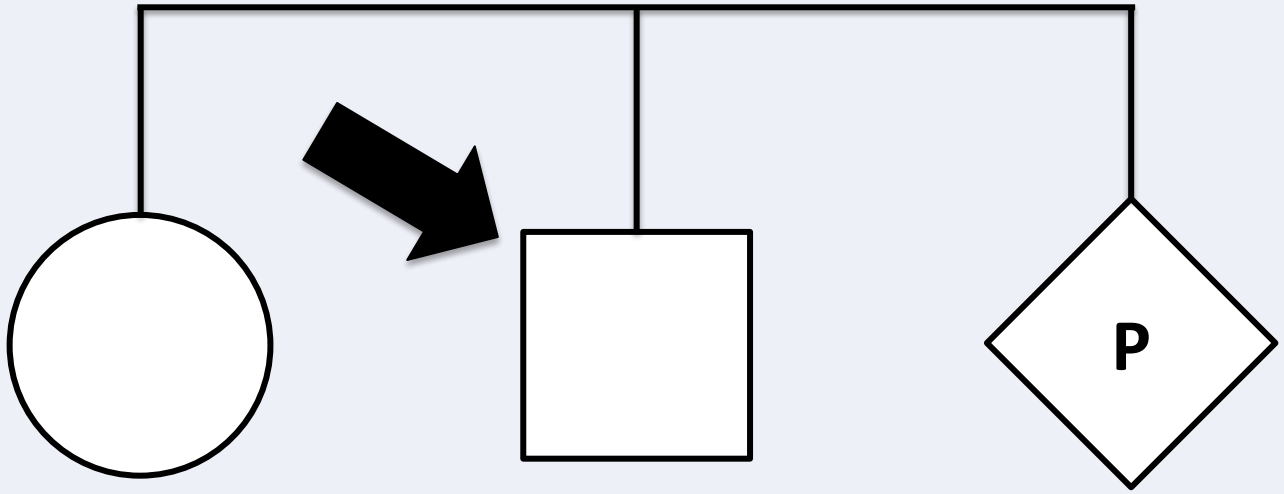
Smith
E. McMurtry & J. Miladinovic
April 2022



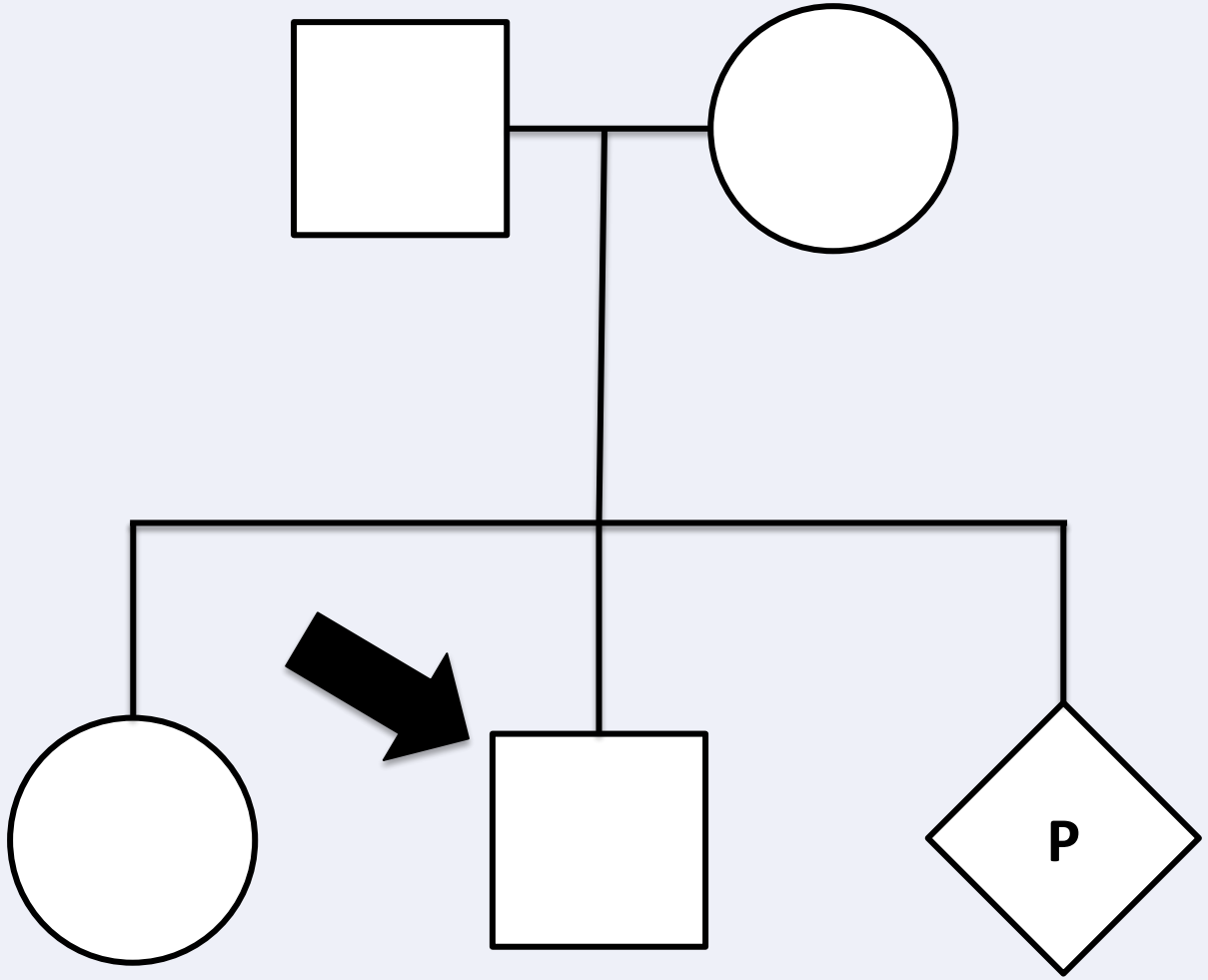
Billy's pedigree

- Using all of the basics of pedigree drawing, let's construct Billy's pedigree!
- Pause the video and use the provided copy of the family history form if you want to practice your pedigree-drawing skills
- Afterwards, we'll walk you through the steps

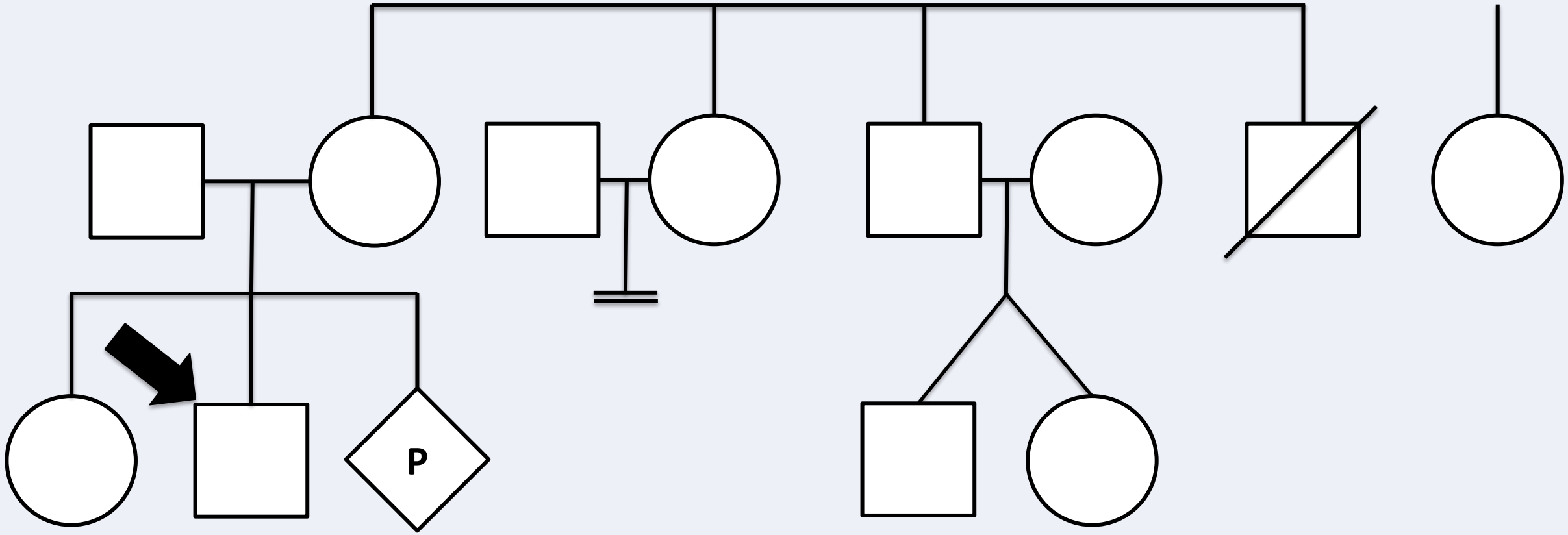
Billy and his siblings



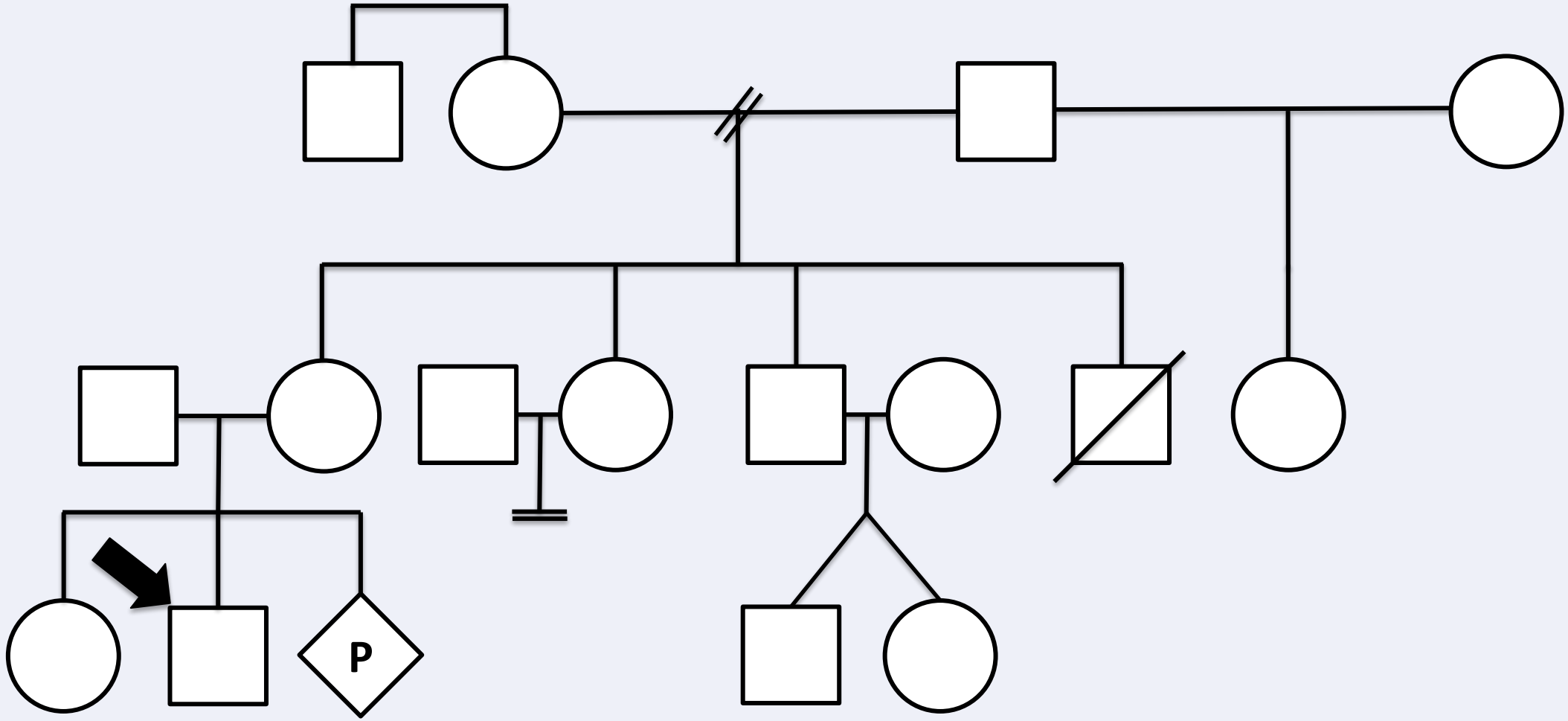
Billy's parents



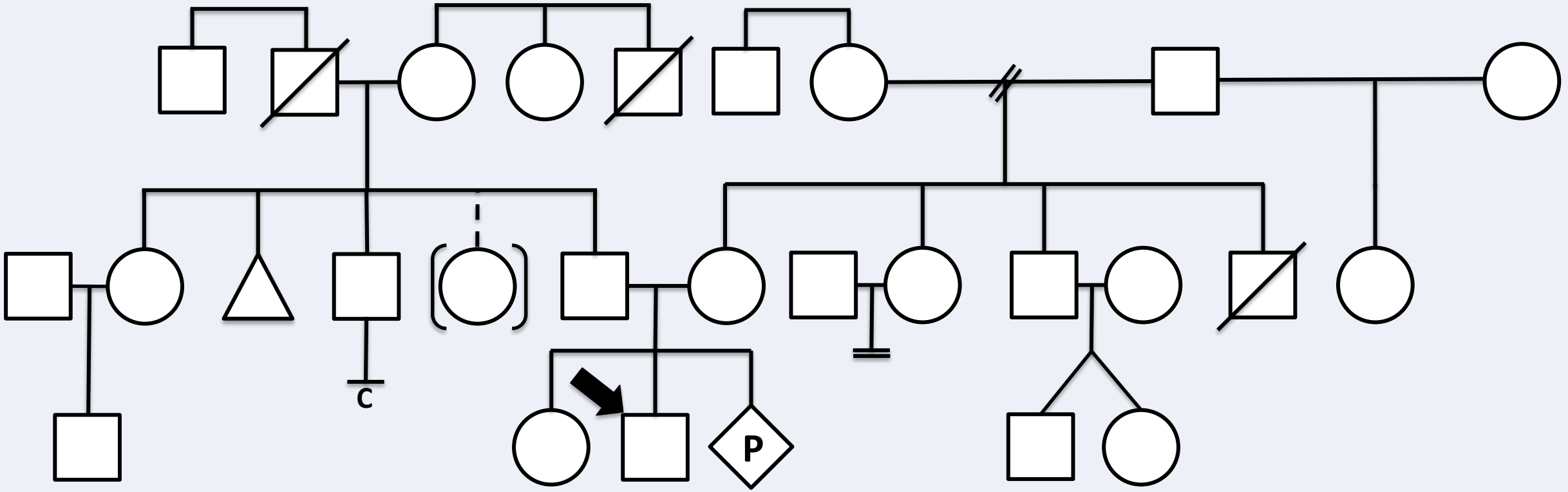
Billy's maternal aunts, uncles, cousins



Billy's maternal grandparents



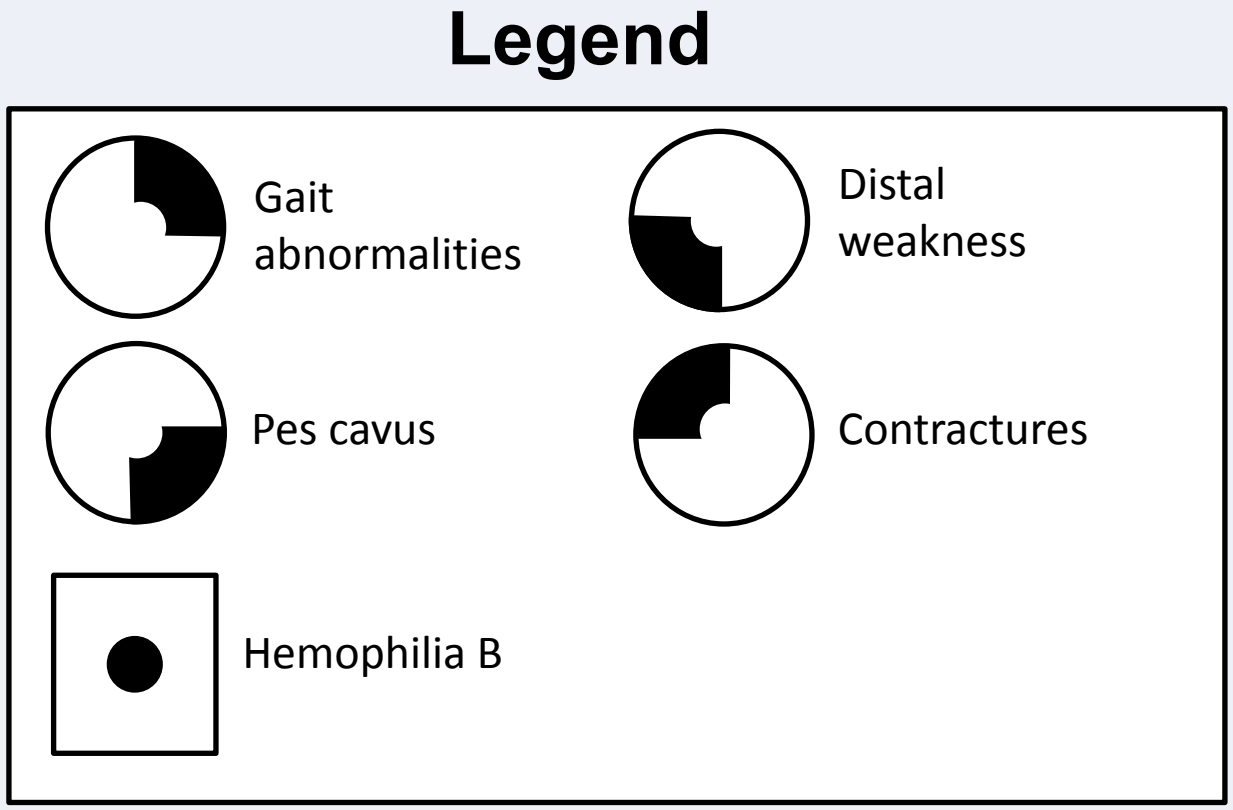
Paternal side of pedigree

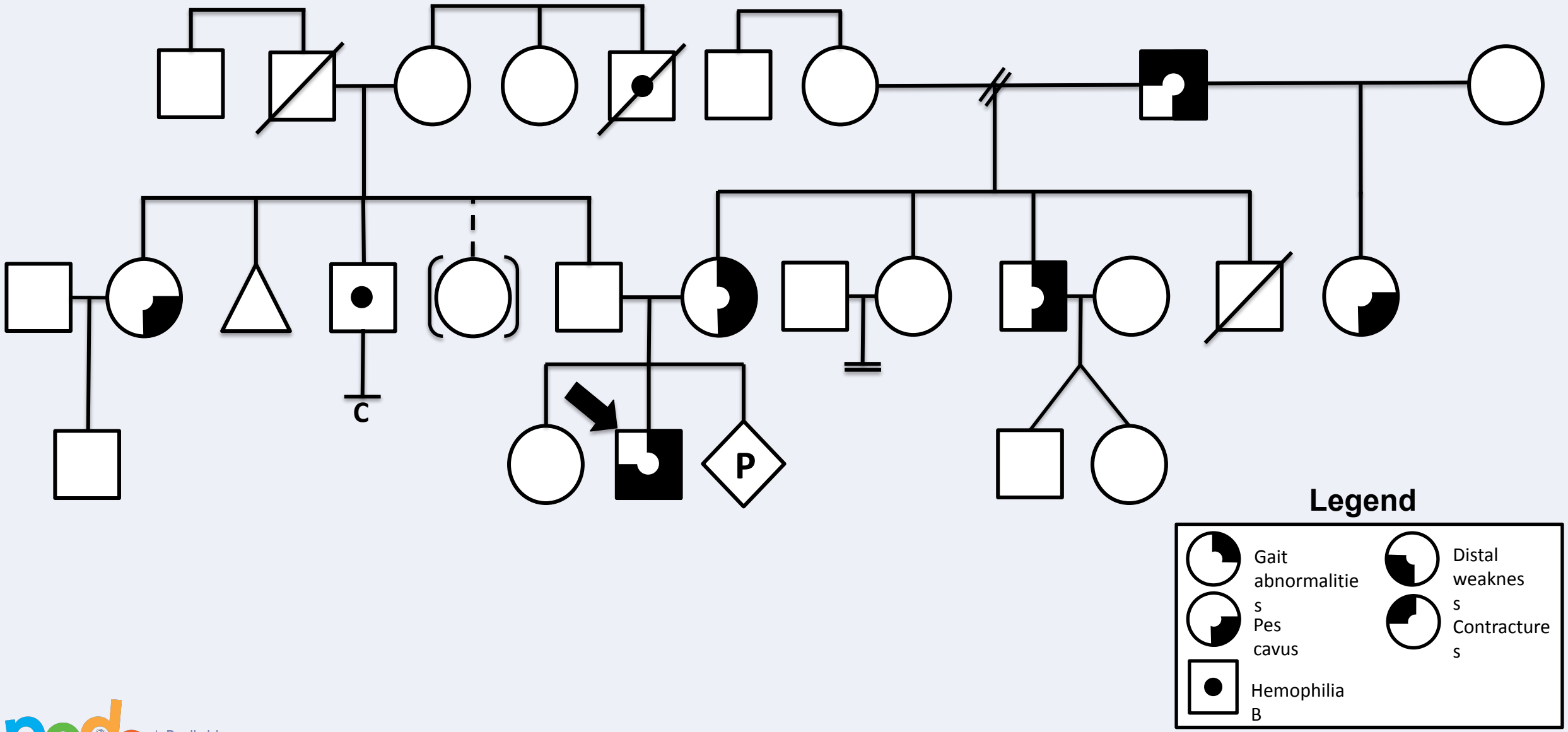


Filling in the details

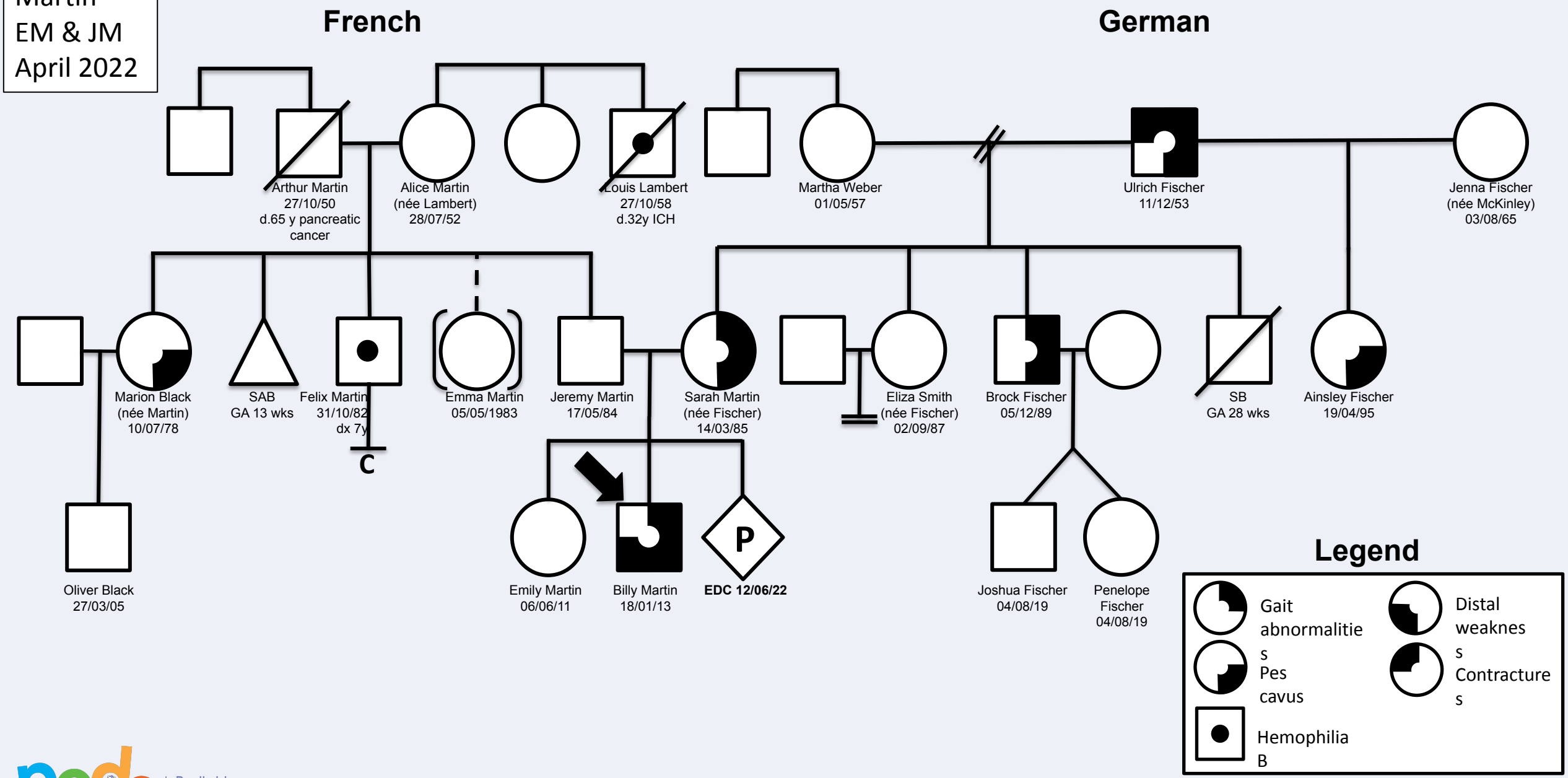
- Which traits would we like to display on the pedigree?
  - Starting with Billy, we've got:
    - Gait abnormalities
    - Pes cavus
    - Distal weakness
  - Other notable traits in the family include:
    - Contractures – in Billy's maternal grandfather – may be related to Billy's condition
    - Hemophilia B
- How do we show these 5 distinct traits, given that an individual can have more than 1 trait?

One way to show these traits:




C
P
Legend
Gait abnormalities
Pes cavus
Hemophilia B
Distal weaknes s
Contracture s

Martin
EM & JM
April 2022



References

1. Tarini BA, McInerney JD. Family history in primary care pediatrics. Pediatrics. 2013 Dec;132(Suppl 3):S203-10. doi: 10.1542/peds.2013-1032D. PMID: 24298128; PMCID: PMC4075136.
2. Trotter TL, Martin HM. Family history in pediatric primary care. Pediatrics. 2007 Sep;120 Suppl 2:S60-5. doi: 10.1542/peds.2007-1010D. PMID: 17767006.

Interpreting Pedigrees – Part II

Learning objective

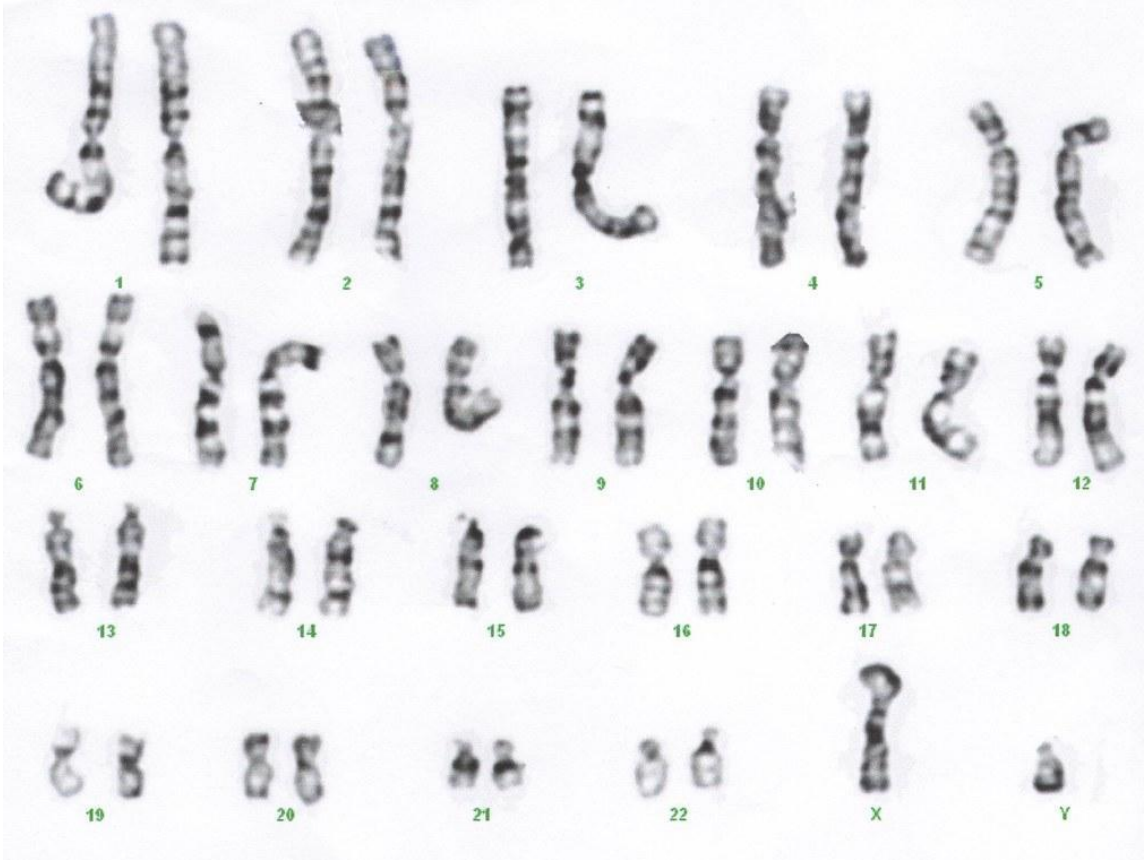
4. Discuss the classic patterns of Mendelian inheritance (autosomal dominant, autosomal recessive, X-linked recessive and X-linked dominant inheritance) and recognize these patterns in a pedigree.

Questions we'd like to answer

- Does Billy's disorder seem to be inherited?
- If so, what mode of inheritance do we suspect?
- What kind of diagnostic testing does the family history prompt?
- What are the implications for Billy's other family members?

Patterns of inheritance

- Each parent contributes a haploid gamete which has 23 chromosomes child has 46 chromosomes in total (23 pairs)
  - 44 non-sex chromosomes (i.e. autosomes), 2 sex chromosomes
- An individual has 2 copies of each gene; one from their mother and one from their father
- Each version of a gene is called an allele
  - 2 copies of the same allele individual is ***homozygous***
  - 2 different alleles individual is ***heterozygous***



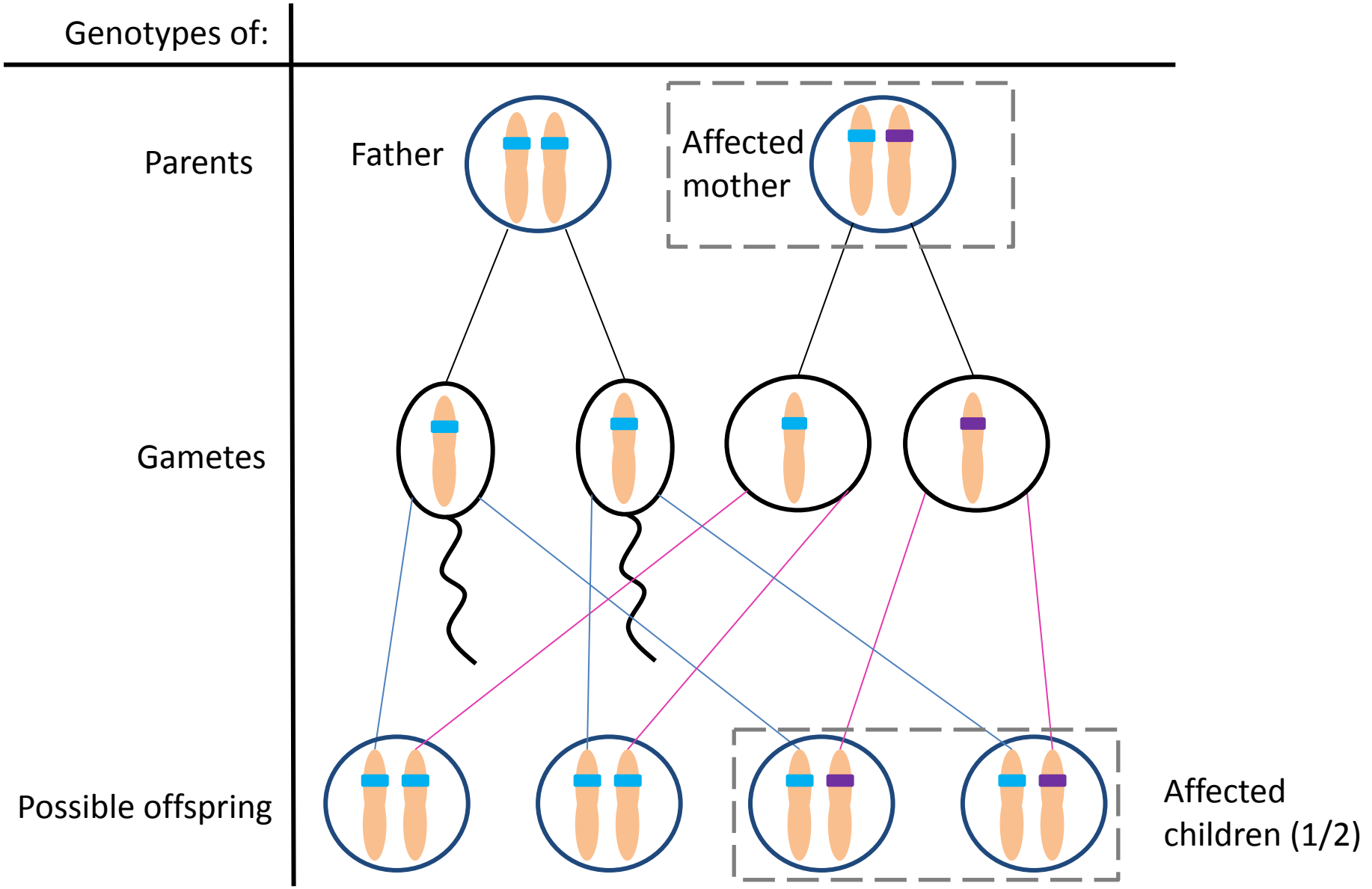
Picture: Karyotype/Can H./Creative Commons

Autosomal dominant (AD) inheritance

Autosomal = The gene is located on an autosome (non-sex chromosome).

Dominant = If even one copy of the allele is present, it will be expressed.

Autosomal dominant (AD) inheritance



AD inheritance rules

Either parent can transmit the trait.

Male and female offspring are affected equally.

The phenotype will likely appear in every generation.

- *There are a few notable exceptions to this rule*

Exceptions to the AD inheritance rules

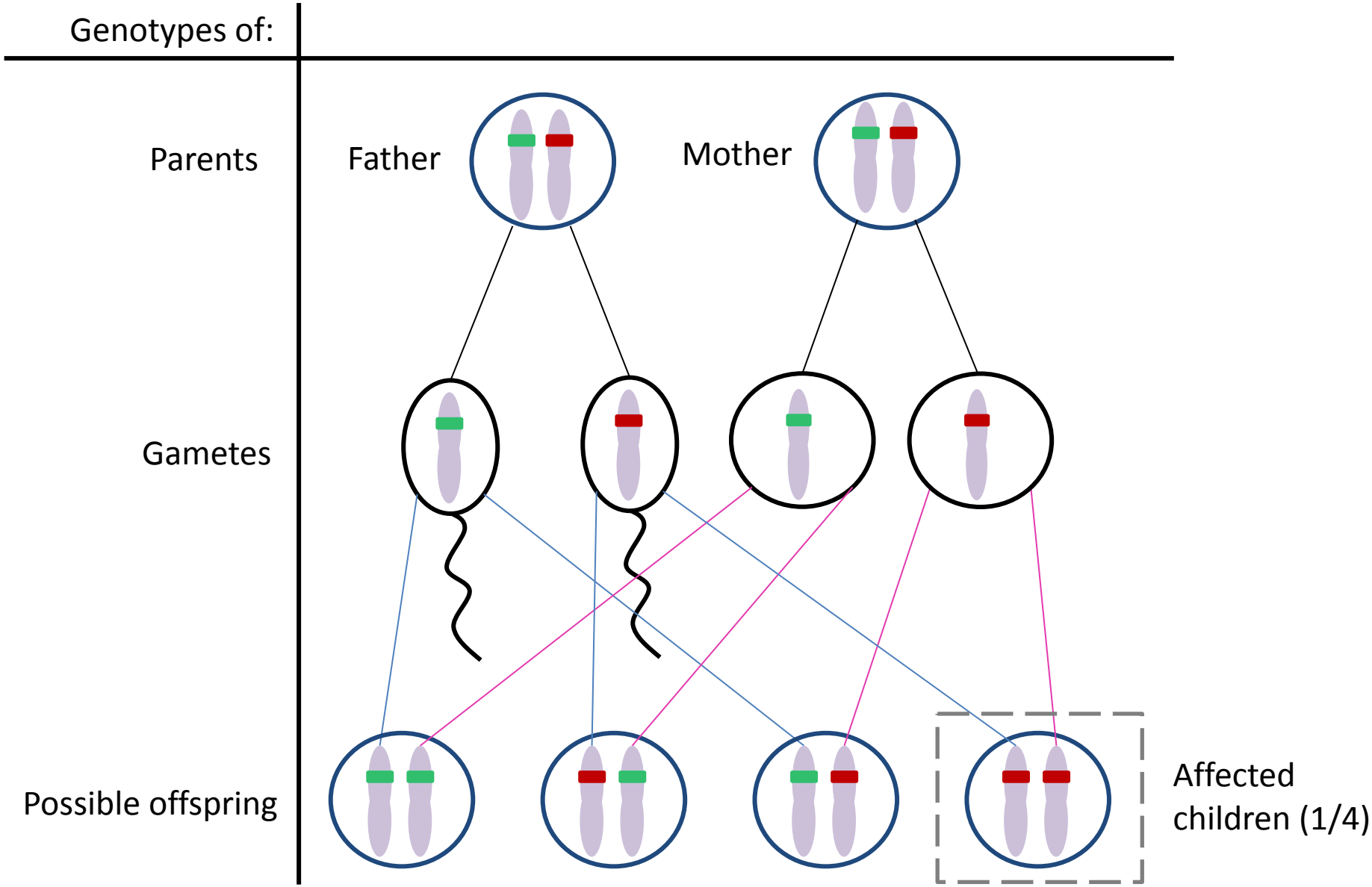
1) De novo mutations.
   - An isolated case might be a new mutation, which can then be passed down to their offspring.
2) Incomplete penetrance.
   - Not everyone who inherits a gene will express it, but the gene can still be passed down to their offspring.
   - Penetrance: proportion of people with the genotype who will express the phenotype.
3) Variable expressivity.
   - Not everyone who inherits the gene will have the same characteristics.
4) Gonadal mosaicism.
   - A person may make some gametes that have the gene mutation, and some gametes that don't. The person can be unaffected but have affected offspring.

Autosomal recessive (AR) inheritance

Autosomal = The gene is located on an autosome (non-sex chromosome).

Recessive = Two copies of the allele are needed to express the phenotype (one from each autosome).

Autosomal recessive (AR) inheritance



AR inheritance rules

Children who are affected typically have unaffected (carrier) parents.

Affected individuals often have unaffected children. They would only have affected children if their partner is a carrier.

The risk of an AR condition increase with consanguineous parents.

People in certain ethnic groups have a higher risk for some AR disorders because the recessive allele is more prevalent within this group.

Exceptions to AR inheritance rules

If an AR condition is common (many people are carriers), the inheritance pattern may be atypical for AR inheritance and the prevalence may be higher than we expect.

Pseudodominance: If a person affected with an AR condition has a child with a carrier, it may look like an AD pattern.

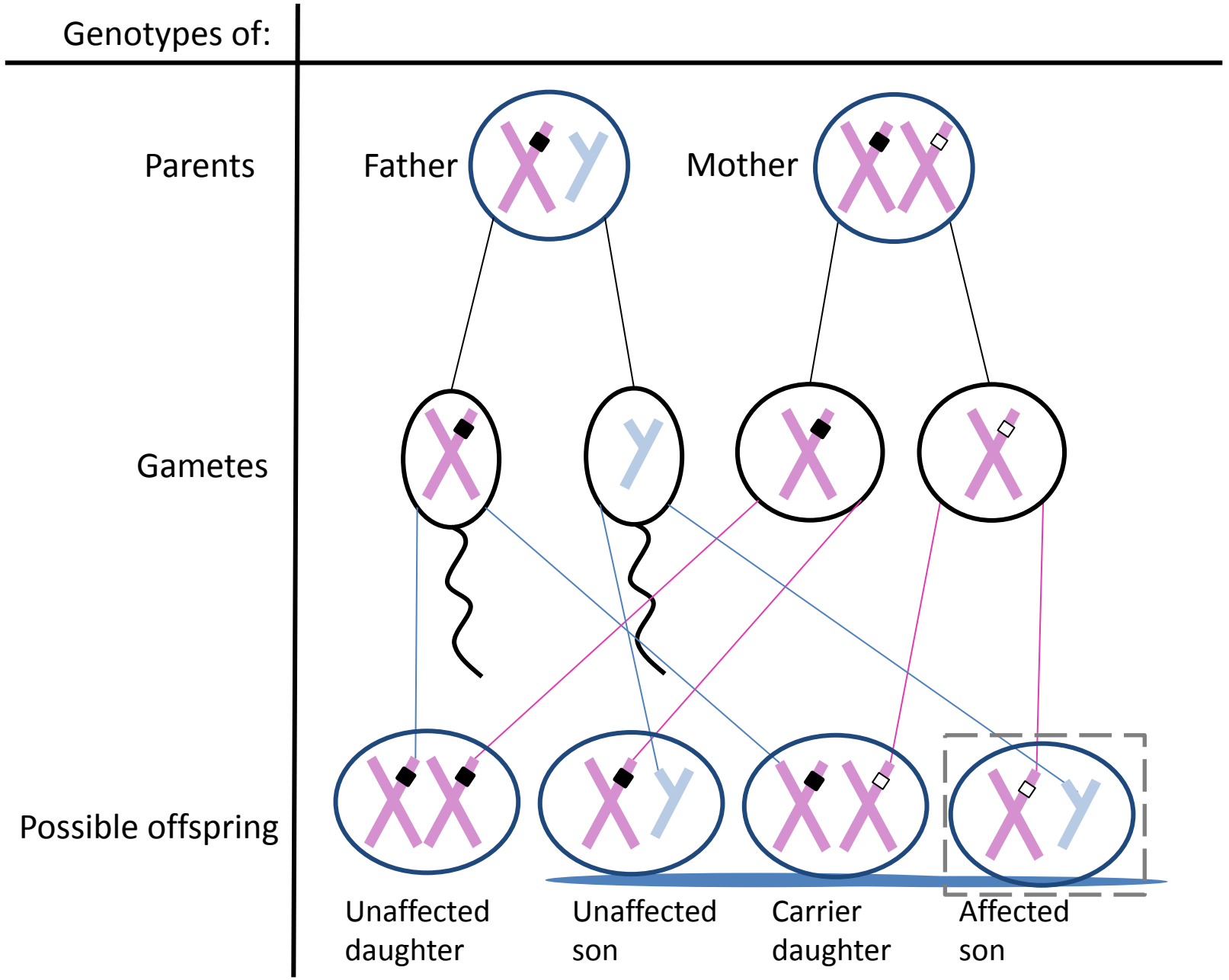
Uniparental disomy: Due to errors in segregation, a child can receive 2 copies of a chromosome from the same parent, which means that a carrier parent can have an affected child.

X-linked recessive inheritance

X-linked = The gene is located on the X-chromosome.

Recessive = The allele will only be expressed if there is no "normal" copy. A female would need two copies of the allele to express the phenotype, while a male would need only one (as he has only one X chromosome).

X-linked recessive inheritance



XR inheritance rules

XR conditions mostly affect males.

Only females can be carriers of an XR condition.

There is no father to son transmission. A daughter of an affected male will be a carrier (unless her mother is a carrier). A son of an affected male will be unaffected.

Exceptions to XR inheritance rules

If there is skewed X-inactivation, one X chromosome is expressed more than the other. A female with one copy of an XR gene may express the phenotype.

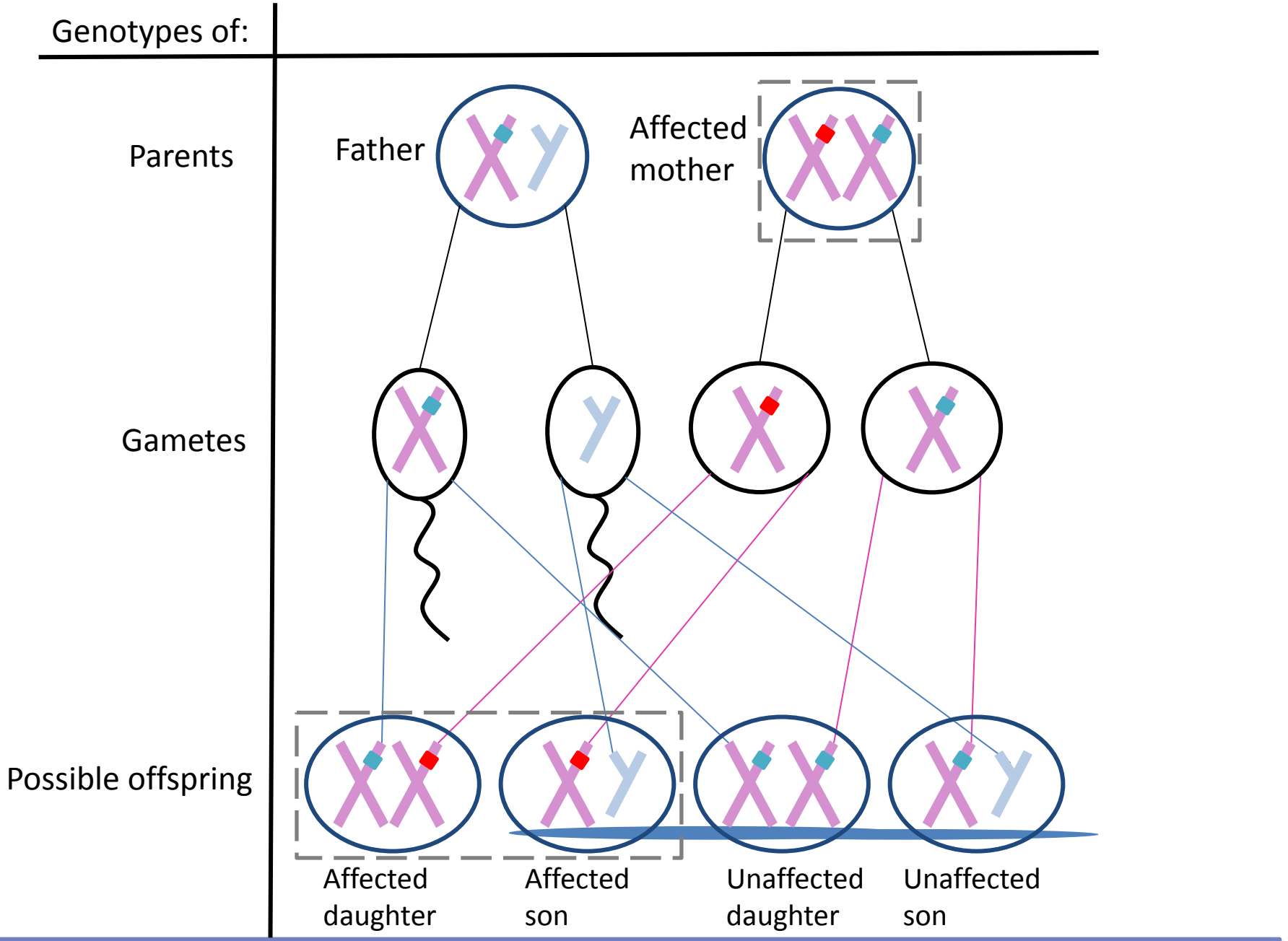
In Turner syndrome, a female is missing or partially missing one X chromosome. A female with one copy of an XR gene may express the phenotype.

X-linked dominant inheritance

X-linked = The gene is located on the X-chromosome.

Dominant = Only one copy of the gene is needed to express the phenotype.

X-linked dominant inheritance – *affected mother*



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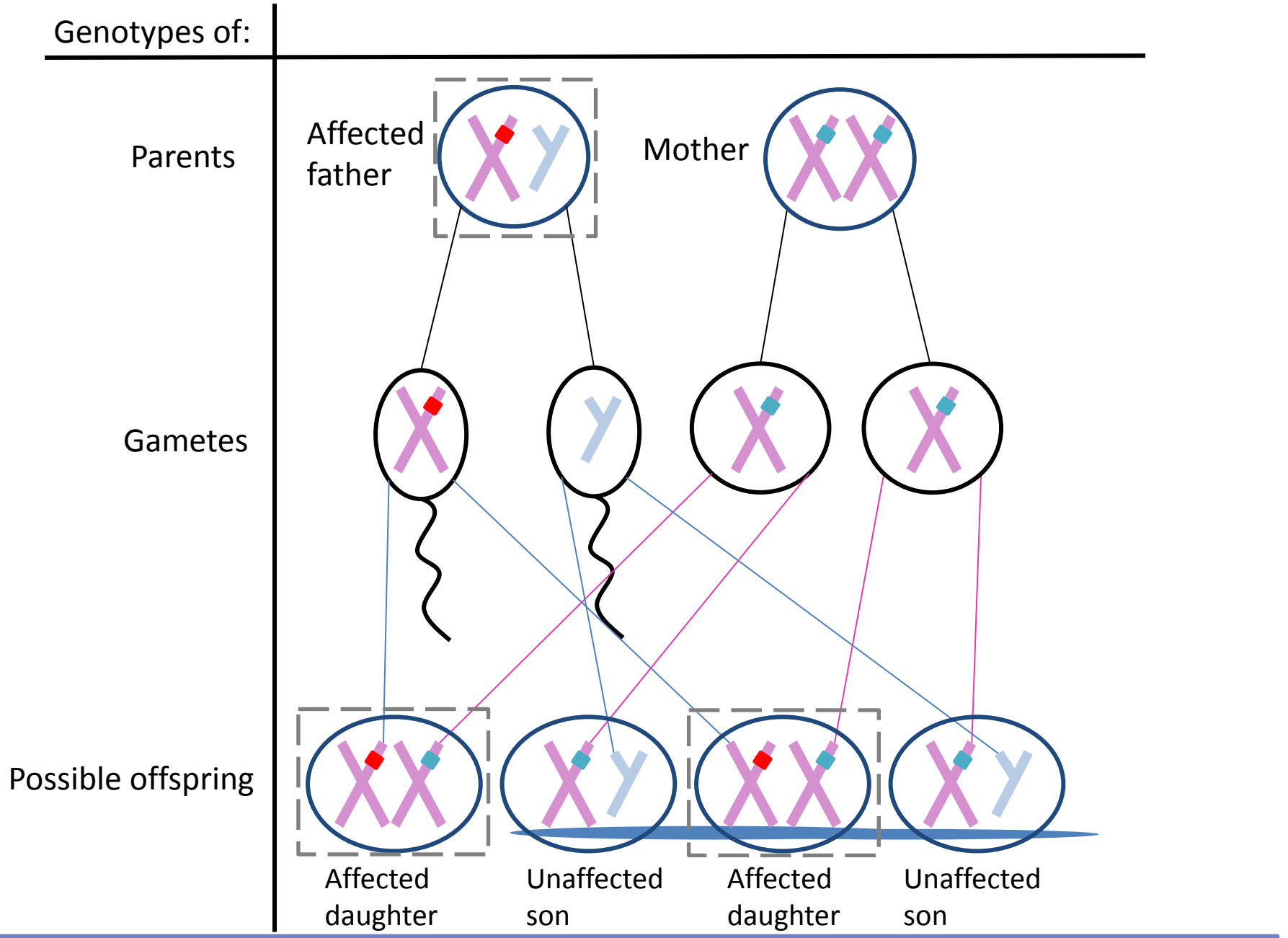
X-linked dominant inheritance – *affected father*



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Recognizing patterns of inheritance in pedigrees

Using simple cases, we will examine what these patterns of inheritance might look like in a pedigree.

To practice on your own, pause the video before we discuss the answers.

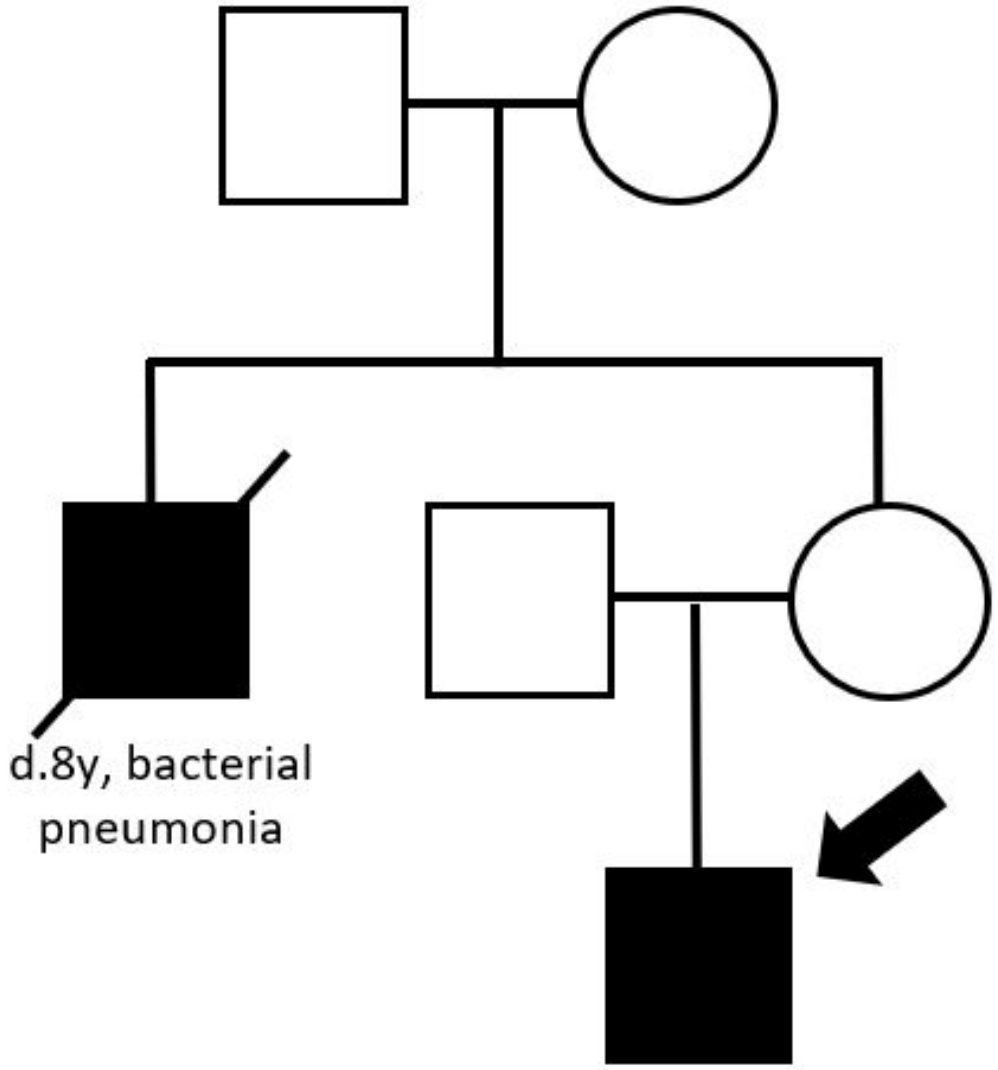
Case 1: David

ID: David, male, 3y old.

CC: Severe recurrent bacterial infections beginning at 6 months of age.

Family history:

- maternal uncle with severe childhood infections, died of bacterial pneumonia at age 8


d.8y, bacterial
pneumonia

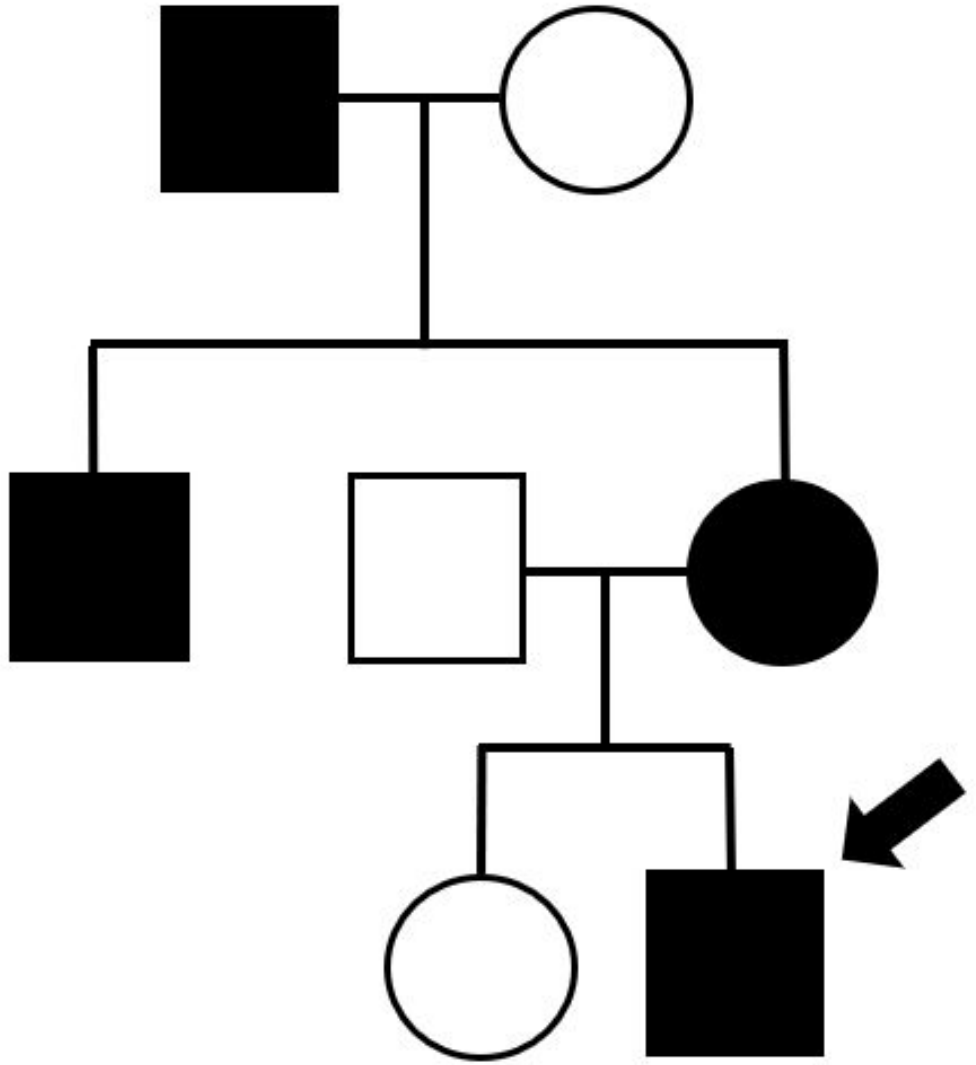
Case 2: Sam

ID: Sam, male, 10y old.

CC: Frequent fractures.

Family history:

- maternal grandfather with multiple fractures in childhood
- maternal uncle with multiple fractures in childhood
- mother with multiple fractures in childhood
- sister (age 16) has no history of fracture



Case 3: Jane

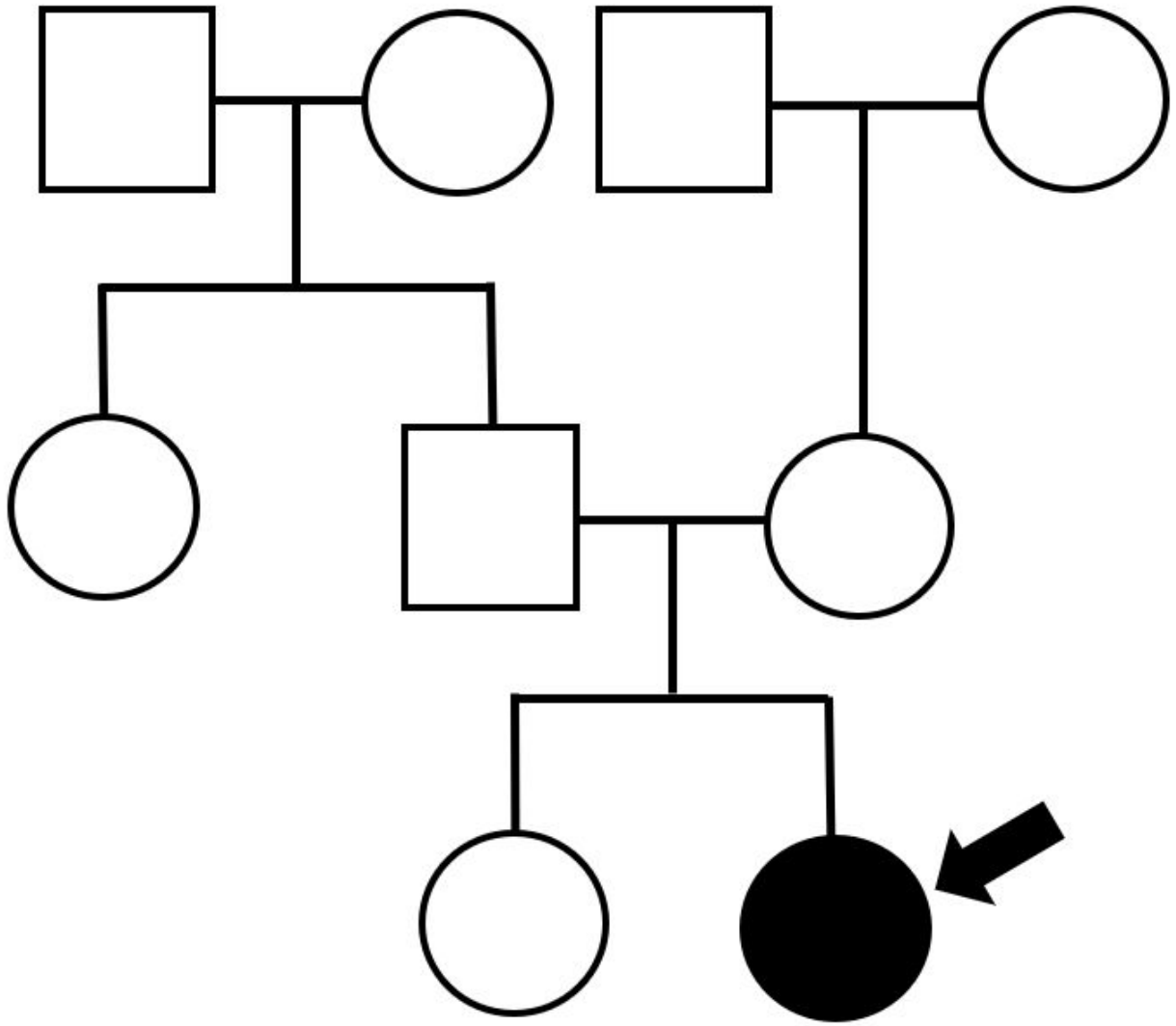
ID: Jane, female, 1y old.

CC: Frequent and severe respiratory illnesses, pale and loose stool.

Family history:

- No affected family members
- Sister (age 8) is healthy

Physical exam: poor growth, wheezes bilaterally, coughing.



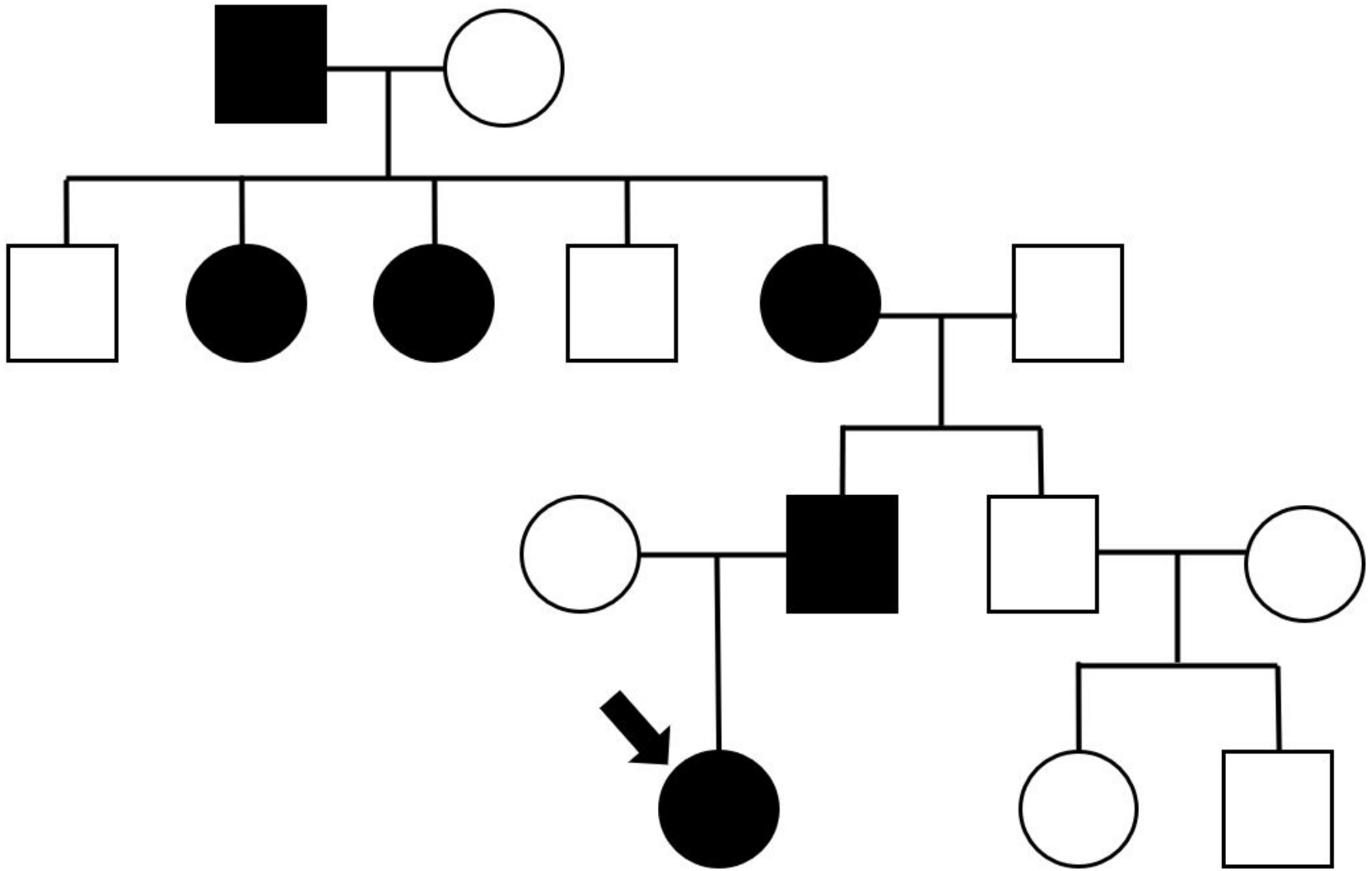
Case 4: Gloria

ID: Gloria, female, 2y old.

CC: Bow-legged, delayed motor development (walking).

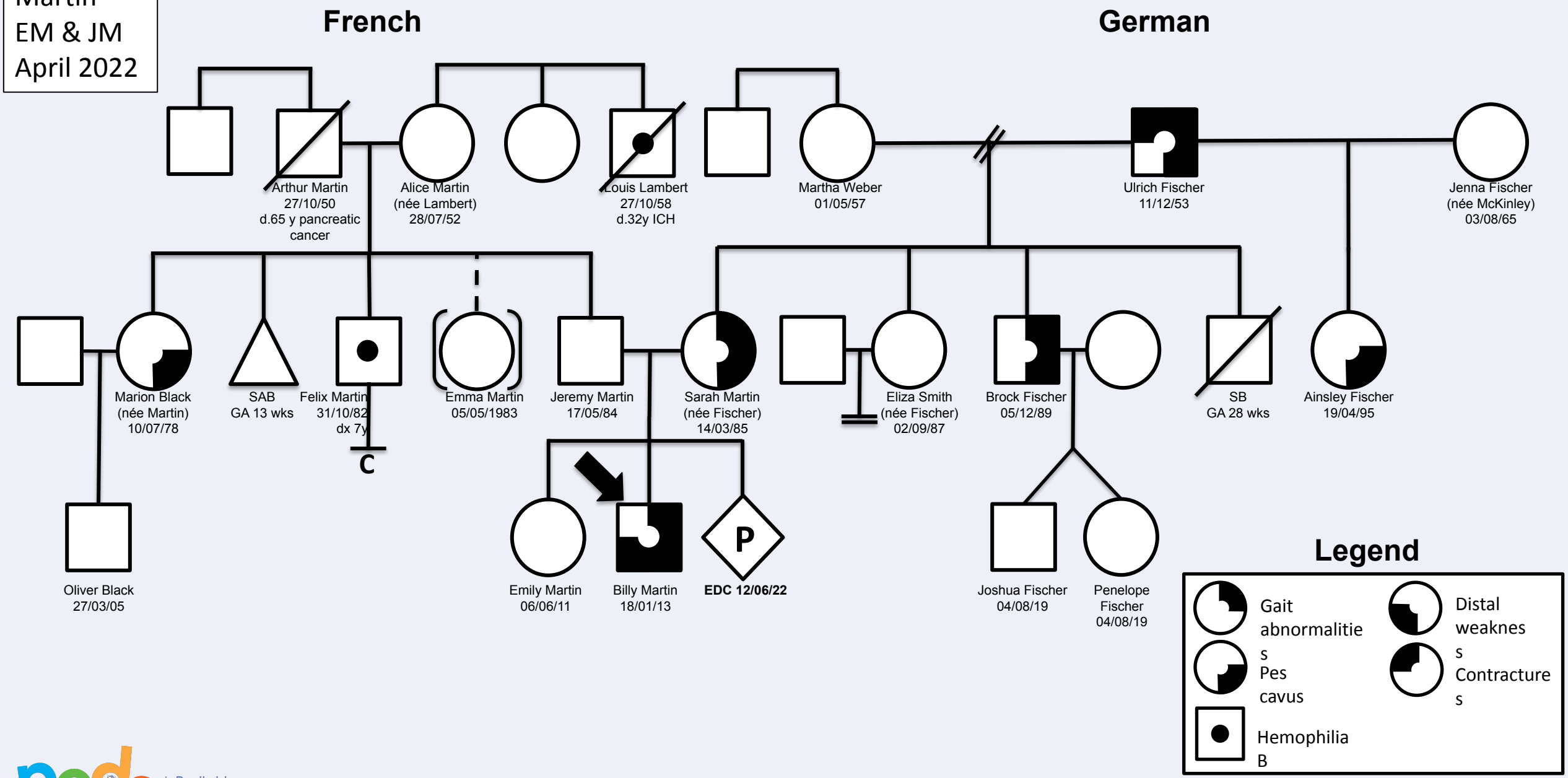
Family history:

- Father is bow-legged
- Paternal grandmother is bow-legged
- Paternal great-aunts are bow-legged
- Paternal great-grandfather is bow-legged



Back to Billy's pedigree

Martin
EM & JM
April 2022



Conclusion

- Billy was diagnosed with Charcot-Marie-Tooth (CMT) disease following assessment by a neurologist, nerve conduction studies, and CMT genetic testing
  - The mutation is in CMT1A – this is an autosomal dominant mutation on chromosome 17
- Charcot-Marie-Tooth disease is a group of genetically heterogenous disorders with a common clinical phenotype
  - Disease onset is usually in the first 2 decades of life, involving symptoms such as distal muscle wasting, weakness, and sensory loss
  - Some variants, like CMT1A, display variable expressivity
  - Treatment is symptomatic and requires a multidisciplinary team
- Billy began working with a multidisciplinary clinic to access physiotherapy, occupational therapy, and receive appropriate orthotics

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