Approach to the Family History and Pedigree

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PART 1

Introduction:

My name is Erinna McMurtry. I'm Jovana Miladinovic. We're third year medical students at the University of Saskatchewan. This is a two-part video that aims to discuss the importance and relevance of family history and how it can be used to construct a pedigree. We'll also review the basics of Mendelian inheritance and how we can see patterns of inheritance in a pedigree. These videos were created in collaboration with Dr. Patricia Blakley, who is an Associate Professor at the Department of Pediatrics at the University of Saskatchewan with specialization in clinical genetics and developmental pediatrics.

Learning Objectives

By the end of Part I, you should be able to:

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.

By the end of Part II, you should be able to:

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.

Our case

To help ground this topic in some context, we'd like to introduce you to a patient, Billy, who we'll follow throughout these two videos.

During your rotation in a family medicine clinic, you meet 9-year-old Billy, who has been brought in by his mother with concerns of frequent sprained ankles over the past couple of months. His mother says he has been tripping and falling over more than usual, and sometimes he appears to be "dragging his feet". She says that Billy has always been a "clumsy kid," but has otherwise been healthy. He was a full-term infant with no pre- or perinatal problems. His development has been normal, except for gross motor delay with concerns with his balance.

On physical exam, Billy appeared well with normal vital signs and growth parameters. Cranial nerves II-XII were intact. His deep tendon reflexes were normal, and no clonus was noted. He had good muscle bulk and tone. Strength was 5/5 throughout, with the exception

of his ankle dorsiflexors, which were graded 4/5 bilaterally. Sensory exam was normal. Upon assessing his gait, bilateral foot drop was noted. Notably, Billy also had high arches (pes cavus).
Apart from referring him to a neurologist for further testing, what else can we do at this point? What other history would be relevant to elicit?

Objective #1: The importance of Family history

After collecting a more detailed HPI for this patient, a key piece of the puzzle could be the family history. The family history has been called the first genetic test; it was - and still is - a valuable tool which can help us recognize susceptibilities, traits, and disorders which run in families and may pose a risk to our patient.[1] The information gleaned from a family history can contribute to our clinical picture and inform appropriate next steps.

Family history can, for one, help us gauge risk. For example, we can get a sense of the likelihood that a patient's symptoms are caused by an inherited disorder, or the likelihood that a patient will go on to develop a particular condition. Especially in a pediatric patient like Billy, a timely and accurate diagnosis could have implications for his medical care for the rest of his life.

Family history can also help us tailor follow-up investigations. Just like the rest of the history and physical exam, it can influence our clinical suspicion and decision-making. It may lead us to order certain clinical, biochemical, and/or genetic tests. As our genetic testing options improve and expand, we must be able to identify patients or families for whom testing or intervention would be relevant and beneficial.[2] A shotgun approach to genetic testing is not feasible, ethically or economically. For example, based on what we know about Billy right now, it wouldn't be appropriate to jump right to ordering a battery of genetic tests. Family history is thus an important tool in helping us choose investigations that are most likely to yield diagnostic or otherwise useful information.

A complete family history can assist in preconception counseling, which has the goal of reducing chances of poor perinatal outcomes by addressing risks prior to pregnancy. If we can identify genetic risk factors, couples can be referred for genetic counseling where they may undergo carrier testing. This can help them make informed decisions about future pregnancies. If we suspect that Billy has a genetic condition, it could have implications not only for any children he might have, but for his siblings, potential future siblings, and other members of his family that may carry the same gene.

A family history can also help guide next steps after a diagnosis of a genetic condition. If Billy is diagnosed with a genetic condition, other family members may carry the same gene and it would be appropriate to offer genetic testing for them as well.

It is also important to remember that families share not only genetic makeup, but also environmental and lifestyle factors, all of which have an impact on health. For example, families may have an increased susceptibility to disorders like diabetes or hypertension, which are rarely caused by a single gene. Nevertheless, knowing about such a susceptibility from a family history can help us recommend lifestyle measures, increased surveillance, diagnostic testing or even intervention. In this way, family history can be a powerful tool for preventative medicine.

The process of asking questions about family history can sometimes be invasive, but it also provides an opportunity for building rapport with a patient or their parents. It can foster a feeling of partnership while also empowering individuals to take responsibility in the management of their own health.

Now that we've outlined why family history is a valuable tool, questions that follow naturally are: when, and how. When is it appropriate to take a family history? How do we go about it? What kinds of questions are we interested in?
We suggest taking a comprehensive family history on initial assessment of all new patients, and then updating it on an annual basis. A comprehensive family history spans 3 generations and includes details on first-, second-, and third-degree relatives. This can provide us with pertinent positives and negatives. Even unaffected family members can help us determine whether a genetic disorder is random, a de novo mutation, or inherited across generations. There are strategies that can help us capture all of the relevant information - for example, we can ask patients to fill out take home questionnaires which can be discussed at subsequent visits if information of concern is identified. The SCREEN mnemonic can help us remember relevant points to inquire about when gathering a family history. It stands for: some concern, reproduction, early disease/death/disability, ethnicity, and non-genetic factors.[1,2]

The questions this should prompt us to ask are:[1,2]

- SC - some concern - Do you have any concerns about diseases or conditions that run in the family?
- R - reproduction - Have there been any problems with pregnancy, infertility, or birth defects in your family?
- E - early disease, death, or disability - Have any members of your family died or become sick at an early age?
- E - ethnicity - How would you describe your ethnicity?
- N - non-genetic - Are there any other risk factors that run in your family?

When asked these questions, Billy's mother, Sarah, reports that:

- Some concern - She is wondering if Billy's symptoms might be related to a disorder that runs in the family, as her father has had gait issues. During Billy's assessment, Sarah mentions that she has high arches as well, and you note that she appears to have a similar gait. Sarah believes that her husband has said that hemophilia B runs in his family
- Reproduction - Her sister and her husband have struggled with infertility. Sarah is currently pregnant.
- Early disease/death/disability – Sarah's father developed gait disturbance in his early 20s, which was never formally investigated but has progressed slowly over decades. He also had high arches and now uses a walker due to stiffness, weakness, and pain later in his life. Billy's paternal uncle was diagnosed with hemophilia at a young age.
- Ethnicity - Her family is German, and her husband's family is French.
- Non-genetic - Billy's paternal grandfather died of pancreatic cancer.

In Billy's case, both his clinical presentation and the family history increase suspicion for a genetic condition. Given this, we would next ask the patient's caregiver fill out a more extensive form detailing the health information of the patient's 1st, 2nd, and 3rd degree relatives so that we can construct a pedigree. For each of these family members, we are interested in their health status, including any health issues and date of diagnosis, dysmorphic features,

developmental issues, and cause and age of death. We also want to know about pregnancies and any fertility issues in the family. The specific family history form that a patient or caregiver would fill out might differ slightly depending on where you work.

On the slide, you'll find the beginning of Billy's form. Attached to this video is a pdf document with the entire completed family history form, which you can use to draw a pedigree or follow along as we do so.

Objective #2 - Pedigree notation

Creating a visual representation of a family history can help a clinician determine whether there could be a genetic component to a patient's presentation, and to see if there are any clear patterns across generations. A pedigree can also help us to detect and connect traits that could be related to a genetic syndrome. Ideally, the pedigree will refine our differential diagnoses and guide our next investigations.

Consistent and universal notation can ensure that anyone who sees the pedigree will understand what it means. There are minor variations to this notation based on individual preference or the standards of a facility or health authority, or to include information that would be important for a particular case. However, there are certain symbols and conventions that we need to be able to use and understand to work with pedigrees.

Basics

- Each family member on a pedigree is represented by a shape. Males are represented by squares, females by circles, and diamonds mean that the sex is unknown or unspecific.
- If these shapes are not filled in, that indicates that the person was "unaffected" by whatever trait we are looking at.
- There are many different ways to indicate the presence of traits or conditions that we are interested in, but essentially we just want to have a different pattern for every trait. For example, we could say that the right upper quadrant being shaded in indicates blue eyes, while the right lower quadrant indicates blond hair. Every person on the pedigree who has blue eyes should have a shaded-in upper right quadrant. Someone could hypothetically have one or both traits, and we should be able to tell this from their symbol. We include each trait and the pattern we use to represent it in a legend at the bottom of the pedigree.
- We need to indicate the "proband" or "index patient", the person that we are taking this history for. We use an arrow to point them out on the pedigree. Under each symbol on the pedigree we can include details that we know and think are important, like birthdate, date of death, or current age, names or initials, and diagnoses and age of onset. Here are a couple of examples.

Lines

- As we are constructing a pedigree, we need to indicate how people are connected to one another.
- A relationship line is horizontal and connects two shapes at their midpoints. In a relationship between one male and one female, the male is placed on the left.
- If this relationship produced offspring, there is a vertical "line of descent" from the centre of the relationship line to the mid-point of the offspring symbol or the sibship line, which is used when there are siblings.

- The “sibship line” is horizontal, and each child’s “individual line” descends from here. The siblings are arranged left to right from oldest to youngest.
- If two people are twins, there is special notation for this. For dizygotic twins (non-identical twins), both individual lines share a point of origin, so the lines are diagonal. For monozygotic twins, we add a horizontal line between the two individual lines. If we don’t know whether a pair of twins is mono- or dizygotic, we can use a question mark at the junction of the individual lines.
- If there are multiple unaffected siblings from a relationship, they won’t affect the genetic assessment so can be combined and represented in one symbol with the number written inside. For example, 5 sisters would be a circle with a 5 inside, and 2 brothers and 3 sisters would be a square with a 2 inside and a circle with a 3 inside. We can’t include siblings that are affected in these groupings. A few caveats to grouping siblings: the siblings of the proband are generally good to draw out individually, as well as children who are still young and may just not be symptomatic yet.
- Relationships can be complex. If two people who are related are in a relationship (consanguinity), this is indicated by using a doubled “relationship line.”
- If a relationship is dissolved, we can note this using two diagonal slashes across the relationship line. In most cases, we don’t need to include multiple previous partners if they don’t affect the genetic assessment (for example, if the partner was not related and there were no offspring from the relationship). However, we need to be mindful of the possibility of miscarriages in these other relationships, which would be important to know about.
- If a person has had children with multiple partners, relationship lines can end up overlapping. If the lines overlap, we can clarify the direction of each line by adding a little bump to the line which crosses over.

Pregnancy

- Since it can be important to know about traits like fertility, we can distinguish between having no offspring, having no offspring by choice, and known infertility. A relationship with no children is indicated by a short horizontal line, then we can add a C if we know that it was by choice or use two horizontal lines if there is infertility.
- Additionally, pregnancy outcomes can be important when looking at some genetic conditions. To indicate these details, we can use different symbols for both current pregnancies, and for pregnancies that were not carried to term.
- For a current pregnancy, we add a symbol representing the sex of the fetus (if known), with a letter P in the middle. We can note the approximate current age of the fetus with the date of the last menstrual period, gestational age, or estimated date of confinement (EDC=due date), and also include the karyotype if it’s known.
- To show a pregnancy that was not carried beyond viability (20-24 weeks GA, depending on which definition is being used), we use a triangle and a shortened line of descent. The triangle should be marked as affected or unaffected using the same pattern that we used for the other family members. We can also indicate the approximate gestational age at death and karyotype of the fetus if known. Some people also use shorthand to indicate the outcome of the pregnancy, for example “SAB” for a spontaneous abortion. For a termination of pregnancy (TOP), we add a diagonal line through the triangle. For an ectopic pregnancy, we can say “ECT.”
- For a stillbirth, we can use the usual circle, square, or diamond to indicate sex with a diagonal line through it, indicate stillbirth with “SB,” and include the gestational age at which they were delivered.

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Death

- If a family member has passed away, we put a diagonal line across their symbol, and include the date or age at death and the cause of death if known.

Adoption

- To show that a family member was adopted, we use brackets around the person who was adopted. A solid line of descent indicates the biological relationship between parents and offspring, while a dashed line connects adoptive parents with the adopted person.

Looking at the pedigree as a whole, there are several other features of note. There will be a key or a legend at the bottom of a pedigree to define which trait or condition is represented by which pattern of shading. If it is known, we can also include the ethnicities of each grandparent (Generation I) at the top of the pedigree. At the top, we also want to include the surname of the proband, the date the pedigree was taken, and the identifying details of the person who took it.

Constructing Billy's Pedigree

At this point, we'll use the completed family history form for Billy which is attached here in order to draw the pedigree for this family. You can pause the video and attempt to construct it yourself based on what you have learned thus far.

First, let's start by drawing out Billy and his siblings. He'll be represented by a square, and because he is our proband, we've also got to make sure we draw an arrow pointing to him. His older sister will be on his left. His mother is pregnant, so we'll note that to the right of Billy. Each of these individuals will have an individual line, and then they'll be connected by a sibship line above. Because we're working in PowerPoint, we can shift the symbols around later. If you're doing this on paper, make sure that you leave lots of space around Billy so that all of his family members will fit.

Next, let's add their parents. Their father will go on the left, and their mother will go on the right. They are connected by a relationship line, which is bisected by the line of descent which extends down to Billy and his siblings.

Going through the family history form, the next part is about the mother's side of the family. We can add Billy's maternal aunts and uncles, making sure we leave space for their partners. Don't forget to include the pregnancy resulting in stillbirth. Again, we'll add the individual lines and connect them with the sibship line. Note that Ainsley is a half-sister, so she won't share the sibship line and line of descent with the rest of the maternal aunts and uncles.

Next, we can add partners and resultant offspring. From the family history form, we know that Eliza has a partner, as does Brock. Eliza and her partner have struggled with infertility, so we must note that. Brock and his wife have dizygotic twins, a boy and a girl.

Billy's maternal grandfather was married to his maternal grandmother, but he remarried, and he had a daughter in this second marriage. We will put him in the middle so that we can draw two relationship lines extending from him, noting that his relationship with Billy's maternal grandmother is dissolved.

We can add the lines of descent. Now all that's left is to add the brother of Billy's maternal grandmother.

We'll follow the same approach to build the pedigree on Billy's paternal side. We'll add all the aunts and uncles, and any partners they have, then their children. We'll add the paternal

grandparents, as well as their siblings. Some features to note here are the dashed line and brackets surrounding Emma Martin, who was adopted into the family. Felix Martin has decided to have no children, and there is no mention of him having a partner, so we must mark that. Billy's paternal grandmother had a spontaneous abortion at 13 weeks gestation, so this is indicated with a triangle.
Now that we've got the bones of the pedigree, we must fill in the details. First of all, we have to decide which traits we'd like to display on the pedigree. Of note, Billy has presented with gait abnormalities, pes cavus, and distal weakness. Billy's maternal grandfather developed contractures, and several family members on his father's side have been diagnosed with Hemophilia B. We have identified 5 distinct traits which are worth displaying in the pedigree. There's no right or wrong way of assigning symbols to show traits, as long as the traits are clear. This is what we came up with.
Adding these symbols to our pedigree, we end up with something like this.
Then, we fill in details like names, dates of birth, and diagnoses, with a final pedigree that looks like this! How does yours compare?

Thank you for listening to Part 1 of our video. We hope that you now have an understanding of the importance of taking a family history, as well as the basics of pedigree notation. Head over to Part 2 of our video where we'll discuss patterns of inheritance, and the way that they appear in pedigrees.

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.

PART 2

Welcome back. In the previous video, we talked about the importance of family history as well as how to construct a pedigree. We drew a pedigree for our patient, Billy, based on a family history taken from his mother. In this video, we will review the classic patterns of Mendelian inheritance and see how these patterns might look in a pedigree. We will introduce you to several "mini cases" as practice before going back to Billy's case.

Objective #4a: Patterns of inheritance

Now that we have constructed Billy's pedigree, we must begin to make sense of it in a genetics context - does the underlying disorder truly seem to be inherited? What mode of inheritance do we suspect? What kind of diagnostic testing does the family history prompt?
Furthermore, what are the implications for Billy's other family members? Is his younger sister likely to develop symptoms? How likely are his parents to have another child with a disorder like Billy?
To demonstrate the utility of pedigrees in genetic problem-solving, we'd like to discuss some of the basics of inheritance. In normal inheritance, each parent contributes a haploid gamete which has 23 chromosomes, resulting in a child who has 46 chromosomes in total, or 23 pairs.
There are 44 non-sex chromosomes, which we refer to as autosomes, and 2 sex chromosomes, which are the "X" and "Y" chromosomes.

When we consider inheritance of genes located on autosomes, we think of each person as having two copies of each gene, one from their mother and one from their father. Each version of a gene is called an allele. If both alleles are the same, we call this homozygous, and if there are two different alleles, this is called heterozygous.
For the two sex chromosomes, mothers always contribute an X, while the father can contribute either an X or a Y. Individuals who are genetically female possess two copies of the X chromosome, while those who are genetically male have one X chromosome (from the mother) and one Y chromosome (from the father). This has implications in the presentation of X-linked disorders, which we will talk about later.

In autosomal dominant inheritance, we are talking about the inheritance of an allele of which one copy is sufficient to produce a particular observable trait - which we call a phenotype.

Let's illustrate with an example. Let us say that the purple allele of the gene of interest is dominant and causes a genetic condition. In this case, the mother possesses the dominant purple allele, and is affected by this genetic condition; the father has no purple alleles, so he is unaffected.
Based on the law of segregation, half of the mother's gametes will possess the dominant purple allele, while the other half will possess the blue allele. The father has two copies of the blue allele, which means that all of his gametes will have the blue allele.
When their gametes are combined to conceive a child, there are 2 possible combinations; a child will either receive two blue alleles, or they will have one blue allele and one purple allele - these scenarios are equally likely. Again, a child will be affected if they have one purple allele. Hence, every time this couple conceives a child, there is a 50% chance that this child will have this autosomal dominant condition.

General rules/hints: In autosomal dominant genetic conditions, either parent can transmit the trait, and male and female offspring are affected at the same rate. We tend to see the phenotype appear in every generation. There are a few notable exceptions to this general rule.

1. An isolated case of an autosomal disorder can occur due to a new mutation in a germ cell – a de novo mutation. A de novo mutation can then be passed down to offspring, or if the mutation is associated with reduced reproductive fitness, we may only see the single case.
2. Additionally, genetic changes are occasionally inherited but ultimately not expressed - we refer to this as incomplete penetrance. Penetrance is defined as the proportion of individuals with a particular genotype who express the phenotype. For example, if an allele causing an autosomal dominant disorder is said to have 80% penetrance, 80% of individuals with that allele will show signs of the disorder, while the remaining 20% will not. This is important to note in pedigrees because sometimes an individual who appears unaffected is actually carrying a disease-causing mutation and thus has the potential to pass it down.
3. Variable expressivity is common in autosomal dominant disorders. This means that individuals of the same genotype do not necessarily have the same phenotype; a condition can be associated with a long list of possible features, and each affected individual won't have every single one.
4. In gonadal mosaicism, some of a person's gametes possess a mutation that may not be present in other tissues of the body. This can happen if a mutation occurs in a germ cell that continues to divide - so some of that individual's gametes will possess the mutated

gene, while others will not. As such, the individual is typically unaffected, but may go on to have 1 or more affected offspring.

In autosomal recessive inheritance, two copies of an allele are required to produce a particular phenotype. In other words, if the recessive allele is associated with a condition, an individual has to receive one copy of the recessive allele from each parent in order to be affected by the condition.

In this example, the pathogenic red allele is recessive. The mother and father are carriers because they possess one copy of the recessive allele, so while they aren't affected by the condition, they carry those alleles and have the potential to conceive children who will go on to have the condition.
Their gametes can be combined to produce children with 3 unique genotypes:

- There is a 25% chance that their child will possess two copies of the non-pathogenic green allele, in which case the child is neither affected nor are they a carrier of the red allele.
- There is a 50% chance that the child will have one copy of the green allele and one copy of the red allele. (This is because there are two combinations that result in this genotype; either the father contributes his green allele and the mother contributes her red allele, or vice versa - the end result is the same.)
- There is a 25% chance that their child will receive two copies of the pathogenic recessive red allele, which means that they will be affected.

General rules/hints: In autosomal recessive genetic conditions, children who are affected typically have unaffected (carrier) parents. Affected individuals also often go on to have unaffected offspring - an affected individual can only have affected children if their partner is a carrier. The risk of inheriting an autosomal recessive disorder increases when one's parents are in a consanguineous relationship. Members of certain ethnic groups can also be at greater risk for some recessive disorders by virtue of the recessive allele being more prevalent in their gene pool as compared to the general population.
Common autosomal recessive conditions with high carrier rates can result in a higher prevalence for this condition than we might expect based on the mode of inheritance. In this case, the pattern of affected individuals in a family may mimic the inheritance of an autosomal dominant condition – this is called pseudodominance. This occurs when an affected person has a child with a carrier of the autosomal recessive condition. Another notable exception to these general rules is that of uniparental disomy. In uniparental disomy, an individual receives 2 copies of a chromosome from the same parent, instead of 1 copy from each parent, due to errors in segregation. In this situation, a carrier parent can have an affected child by passing down two copies of the deleterious recessive allele.

X-linked disorders arise from genes on the X chromosome. If a disorder is X-linked recessive, it'll only appear in a female if she has two copies of it. However, because males have only one X chromosome, they will always express the trait associated with a recessive X-linked allele despite only having 1 copy of the gene.
In the example on the slide, the pathogenic white allele is located on the X chromosome and is inherited in a recessive fashion. The mother is a carrier, while the father is unaffected.
Their gametes can be combined to produce 4 unique genotypes, as outlined on the slide. If they have a boy, there is a 50% chance that he is affected. If they have a girl, there is a 50% chance that she is a carrier.

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General rules/hints: X-linked recessive genetic disorders predominantly affect males. Females can be carriers of the disorder, but their second X chromosome which is normal means that they are generally unaffected. If an affected male has a son, he must contribute a Y chromosome - as such, there is no father to son transmission. If an affected male has a daughter, he must contribute an X chromosome which has a copy of the recessive allele, so his daughter will be a carrier.
Exceptions to expression in females can occur if there is skewed X-inactivation, where one of the two X chromosomes is inactivated more than the other, or in Turner syndrome, where one X chromosome is absent.

X-linked dominant inheritance is an uncommon pattern in which the phenotype associated with the allele is expressed in heterozygotes - so in this case, in contrast to the X-linked recessive pattern, a female with just ONE copy of the allele will be affected. As such, each child of an affected mother has a 50% chance of inheriting the trait, regardless of the sex of the child. It is important to note that some X-linked dominant conditions (such as Rett Syndrome) cause male lethality which will lead to an apparent absence of affected males.
However, just like with X-linked recessive inheritance, affected males cannot produce affected sons. All daughters of affected males will be affected.

Objective #4b: Recognizing patterns of inheritance in pedigrees
Next, we'll go through some simplified examples of different types of inheritance using sample cases of real genetic disorders. These cases will be less complex than a pedigree you might see in practice. In real life, patterns of inheritance can be masked and complicated by things such as de novo mutation, expressivity and penetrance, and gonadal mosaicism. In addition, patients may not always know the full medical history of their extended family members, nor even know what details would be important to tell us. As we go through the cases, feel free to pause the video and answer the questions yourself before we discuss the answers.

Case 1: X-linked agammaglobulinemia[1]
For the first case, we have a 3-year-old boy named David presenting with severe recurrent bacterial infections beginning when he was 6 months old. When a family history is taken from his mother, she states that no one else in the family has experienced anything like this except for her brother. Her brother (David's uncle) suffered from frequent and severe infections throughout his childhood and died of bacterial pneumonia at age 8.
Once we have gathered all the information we need about her and her son's family, we can begin to construct a pedigree, looking at susceptibility to bacterial infections as our trait of interest.
Now that we have our pedigree, what kinds of patterns are there? First, we can see that the only affected people are both male, indicating that this could be an x-linked condition. Both affected males have unaffected parents, making it unlikely to be a dominant trait. So, based on this pedigree, we would be suspicious that David has an x-linked recessive condition.
This case was based on "x-linked agammaglobulinemia," which is an immune deficiency that affects males and prevents B cell maturation, resulting in susceptibility to bacterial infection. Other x-linked recessive conditions that you might encounter include red-green colour-blindness, hemophilia, and Duchene muscular dystrophy.

Case 2: Osteogenesis imperfecta[2]

In the next case, you are meeting a 10-year-old boy named Sam accompanied by his mother. Sam has sustained three fractures on separate occasions within the past year. Most recently, he was witnessed tripping during school recess, which resulted in a fracture to his right femur. There is no suspicion of child abuse. On family history, you find out that Sam's grandfather had fractured his legs multiple times when he was younger, but hasn't broken a bone since he was 15. His mother recalls that she and her brother (Sam's uncle) both had multiple fractures in their childhood while playing sports or during normal activities. The patient has a 16-year-old sister who has never broken a bone.
From this information, we will draw out a pedigree using frequent fractures as our trait of interest.

Now, looking at this pedigree, what kinds of patterns can we see? Right away, we can see that there are several family members with this trait. Since it looks like males and females are both affected at similar rates and that the trait can be passed on by a male or female parent, it is likely not going to be an X-linked pattern. We can also see that there are affected people in each generation, and there is no time when an affected offspring has an unaffected parent, increasing the likelihood that this is a dominant trait. From the pedigree, Sam's frequent fractures appear to be inherited in an autosomal dominant pattern.
This case is based on osteogenesis imperfecta type I, which is often inherited in an autosomal dominant pattern. This condition affects collagen, and in Type I OI, frequent fractures are a common presentation. Other AD conditions that you might encounter include Neurofibromatosis type I, Huntington's disease, and Marfan syndrome.

Case 3: Cystic Fibrosis[3,4]
Next, we have Jane, who is a 1-year-old girl brought into clinic by her parents who are concerned that she seems to have frequent respiratory illnesses during which she becomes very sick. They also note that her stool is often pale and loose. They recently immigrated to Canada, so aren't certain what kind of screening tests Jane had as a newborn. On physical exam, Jane appears small for her age, and there are wheezes bilaterally on auscultation of her lung fields. She also coughs several times during the exam.
On family history, you discover that Jane's family are all healthy. Jane has an older sister who is also healthy.
On Jane's pedigree, we can see that there are no affected relatives so her condition could be sporadic. However, given the clinical features of her condition and the fact that the pedigree indicates that it is not a dominant or x-linked condition, we would be highly suspicious of cystic fibrosis. Autosomal recessive conditions often appear as an isolated case, as carriers would generally not be symptomatic and it is statistically unlikely for two carriers of a rare disease to meet and reproduce unless there is consanguinity. If we diagnose Jane with an autosomal recessive condition, we could determine that her parents are both likely asymptomatic carriers of the disease, meaning that there is a 25% risk of any of their future children also inheriting the disease.
This case is based on cystic fibrosis, which is caused by mutations to both copies of a gene for a membrane protein called CFTR. There are a wide range of manifestations, including frequent lung infections, pancreatic insufficiency, and infertility in males. Carriers with only one mutated copy of the gene (like Jane's parents) are healthy, and the carrier frequency in the general population is relatively high. Other AR conditions you might see include sickle cell anemia, hemophilia, and Tay Sachs disease.

Case 4 Hypophosphatemic Rickets[5]

Last but not least, you are seeing a 2-year-old girl, Gloria, in clinic due to her parents' concern that she appears "bow-legged". She started walking somewhat late, at 18 months, as she seemed reluctant to stand up and bear weight. Now that she has been walking, her legs have become increasingly bowed. On family history, you find that bowed legs run in the family - Gloria's father is bow-legged, as is his mother. He recalls that his mother (Gloria's paternal grandmother) mentioned that her father and all her sisters were bow-legged as well. You draw out the following pedigree.

There are several things that we immediately notice in Gloria's pedigree. The trait we are investigating appears in every single generation, which points us towards a dominant condition. An autosomal dominant disorder should affect males and females in the same ratio. In an X-linked dominant condition, we expect half of the children of an affected mother to have the condition, but an affected male will have only affected daughters and no affected sons.
This pedigree is therefore a convincing illustration of X-linked dominant inheritance. The affected male in generation I goes on to have only affected daughters, as he obligately transmits the X chromosome with the pathogenic allele to them. His sons, however, receive a Y chromosome from him and an X chromosome from their unaffected mother, so they are unaffected. Conversely, half of the children of an affected female are affected; Gloria's paternal grandmother has two sons, one of whom is affected. Gloria's father will go on to produce only affected daughters.
After your initial round of investigations, you find that Gloria's serum phosphate levels are low, while her urinary phosphate excretion is high. This is in line with hypophosphatemic rickets, which is an X-linked dominant disorder. Other examples of X-linked dominant disorder that you might encounter include Rett syndrome and Fragile X. Rett syndrome is lethal to males in utero.

Analyzing Billy's pedigree
Now that we have had some practice interpreting modes of inheritance in pedigrees, let's go back to our initial patient, Billy, to assess the pedigree we constructed in the previous video. We'll start by describing any obvious patterns and findings that we can see. Symptoms related to Billy's presentation (like pes cavus, gait abnormalities, and muscle issues) seem to be present mostly in his mother's side of the family. We can see pes cavus in one paternal aunt, but knowing that this case is isolated and that high arches are a relatively common trait, we are still going to focus on the maternal side for Billy's condition. In Billy' mother's family, males and females appear to be equally affected. All affected people also had an affected parent, and there is at least one affected person per generation. There is no consanguinity.
Now, we can work through which modes of inheritance are likely based on these patterns. If the disorder was autosomal recessive, we likely wouldn't see so many affected individuals. We would also expect to see cases where someone with the trait has unaffected parents, who are carriers. If the disorder was x-linked recessive, we would see more males than females being affected, and Billy's mother would be unaffected (unless we ran into the unlikely situation that her own mother was a carrier). If the disorder was x-linked dominant, we wouldn't see any transmission from father to son, which we can see between Ulrich and Brock.
Based on Billy's symptoms and this family history, we would want to test for Charcot Marie Tooth disease - based on our pedigree, it seems likely to be the autosomal dominant variant.

Knowing that this is autosomal dominant can also guide testing and treatment for Billy's other family members. Any siblings of Billy would have a 50% chance of inheriting this condition as well, which has implications for Sarah's current pregnancy. Likewise, if Ainsley and Brock are diagnosed, their children would also have these same probabilities.

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Although the hemophilia B in Billy's father's family does not seem to be related to Billy's symptoms, we can look at patterns here as well. Since both affected family members are male, we are initially suspicious of an x-linked condition. There are affected people with unaffected parents, indicating that is unlikely to be a dominant trait. These patterns verify our knowledge that hemophilia is inherited in an x-linked recessive pattern. Billy's grandmother was likely a carrier and her daughter Marion has a 50% chance of being a carrier as well. Billy's father is unaffected and cannot be a carrier, so cannot pass on this gene to his children. Remember that males cannot be a carrier of an x-linked recessive gene, as if they have only one copy of the allele on their X chromosome, they will display the phenotype. This pattern of inheritance could indicate the need for carrier testing for Marion and testing for any of her children.

Billy was diagnosed with Charcot-Marie-Tooth (CMT) disease following assessment by a neurologist, nerve conduction studies, and CMT genetic testing using a blood sample. He demonstrated markedly slowed nerve conduction velocity, and he was found to have a mutation in the CMT1A gene, which is located on chromosome 17. [6,7]

Charcot-Marie-Tooth disease encompasses a group of genetically heterogenous disorders which have a common clinical phenotype involving motor and sensory neuropathy.[6,8] It is caused by mutations in genes that encode different proteins which are present in various locations like in myelin, Schwann cells, and axons – more than 80 different genes have been found to be implicated in CMT.[6,8] All Mendelian inheritance modes have been described for this disease, with autosomal dominant transmission being most common.[6]

The CMT phenotype arises due to axonal degeneration, resulting in distal muscle wasting, weakness, and sensory loss.[6] Symptoms generally appear in the first 2 decades of life with a slow progression over the years.[6] The CMT1A variant, which Billy has, is associated with a phenotype which is relatively benign compared to other subtypes.[7] Patients usually remain ambulatory throughout their life.[6] CMT1A also shows variable expressivity within families with disease severity differing even between monozygotic twins.[6] This explains the range of symptoms present in the affected family members on Billy's maternal side.

Treatment for CMT should address symptoms such as muscle weakness, balance and mobility impairment, and sensory symptoms and therefore involves management by a multidisciplinary team.[8,9] Billy and his family were referred to a genetic counseling program and a support group. Billy also began working with a multidisciplinary clinic to access physiotherapy, occupational therapy, and receive appropriate orthotics.

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