PedsCases Podcast Scripts

This podcast can be accessed at www.pedscases.com, Apple Podcasting, Spotify, or your favourite podcasting app.

Genetic Diseases 2: X-linked inheritance

Developed by Rozlyn C.T. Boutin and Dr. Caitlin Chang for PedsCases.com.
February 19, 2022

Introduction:

Hi, my name is Rozlyn Boutin and I am a 4th year medical student at the University of British Columbia. This podcast was developed together with Dr. Caitlin Chang, a medical geneticist at the British Columbia Children's Hospital in Vancouver, BC, Canada. Today we will be discussing X-linked patterns of genetic inheritance using a case of X-linked hypophosphatemia as an example. This is the second podcast in a 3-podcast series on Genetic Diseases. For the purposes of this podcast, female will refer to people with XX chromosomes and male will refer to people with XY chromosomes. However, we recognize that people have a range of gender identities that may not align with their sex assigned at birth.

By the end of this podcast, learners should be able to:

1. Define X-linked inheritance.
2. Describe the concept of dosage compensation.
3. Describe the clinical implications of dosage compensation on disease phenotype expression in cases of X-linked conditions in females.

Genetics play an important role in all areas of medicine, from Family Medicine to Ophthalmology, and an understanding of the genetic basis of disease can help to inform choice of diagnostic investigations, recurrence risk counselling, as well as treatment options for patients of all ages. To illustrate, let's begin with another case.

Case

You are a 4th-year medical student working in an outpatient Medical Genetics clinic. You are seeing David, a 5-year-old male referred by his pediatrician for lower extremity bowing noted after he started to walk. David is suspected to have rickets, a skeletal disorder, most commonly caused by vitamin D deficiency. He was seen by Endocrinology and contrary to what would be expected for vitamin-D-deficiency-associated rickets, the workup demonstrated normal calcium and vitamin D levels, but low blood phosphate levels and high alkaline phosphatase. Additional urine studies were done by the endocrinologist, who suspects hypophosphatemic rickets (urine phosphate wasting), but these are not back yet.

Developed by Rozlyn C.T. Boutin and Dr. Caitlin Chang for PedsCases.com.
October 16, 2022.

Your preceptor asks you to get started with taking David's history. As a keen senior medical student, you begin by introducing yourself to the family and gathering some more information about David, including the medical history. You recall from Louise's case that drawing a family pedigree is crucial for identifying the possibility of a genetic disorder in a family. You complete a family history asking for similar symptoms in any family members.

You learn that David has a 3-year-old male sibling. The family wonders if he may have mild bowing of the extremities as well. The mother reports a personal history of short stature, joint stiffness, hearing loss, and multiple cavities. Her mother had similar symptoms and was told as a girl that she had "vitamin D-resistant rickets". David's maternal uncle has also always been shorter than his peers and suffers from joint stiffness and hearing loss. The uncle's two sons, aged 8 and 13 years, are healthy. David's father is healthy, and the paternal grandparents are both alive and well.

As you draw out your pedigree, you review your notes from medical school on Mendelian patterns of inheritance. Medelian disorders are genetic conditions that present with a predictable pattern of inheritance, caused by "variants" or differences in spelling in a specific gene. David's family history may be suggestive of either autosomal dominant or X-linked inheritance. Autosomal dominant conditions affect males and females equally, and are expressed when an individual has a single copy of a pathogenic gene variant on an autosome[1]. These conditions are traditionally characterized by affected family members in multiple generations[1]. On the other hand, X-linked conditions are observed more frequently in males, are caused by variants on the X chromosome, and cannot be transmitted from male to male[1]. Let's review X-linked genetic inheritance in more detail.

X-Linked Inheritance

Recall that all humans have 22 pairs of numbered chromosomes, known as automomes, and one pair of sex chromosomes, which are the X and Y chromosomes. Females have two X-chromosomes, whereas males have one X and one Y chromosome[1]. A woman will pass on one of her two X chromosomes in any given pregnancy, while a man will pass on either an X chromosome (to a daughter) or a Y chromosome (to a son). Therefore, in X-linked inheritance, male-to-male transmission is not observed[1]. On the other hand, all females of an affected male will inherit the X chromosome with the disease-causing variant[1].

X-linked conditions can show dominant or recessive patterns of inheritance[1]. Since males have only one X chromosome inherited from the mother, X-linked recessive pathogenic variants will be expressed in all males with the variant, and carrier females may be mildly or unaffected[1]. By contrast, X-linked dominant conditions typically present only in affected females, with male lethality[1]. Other conditions may present similarly in both females and males. Some experts suggest that these conditions be termed "X linked" rather than "X-linked dominant or recessive."

Female carriers of X-linked recessive conditions can have unexpected presentations. For an autosomal recessive condition, a carrier of only one genetic change would not express symptoms. However, with X-linked conditions, female carriers can have variable symptoms.

Developed by NAME and NAME for PedsCases.com.
October 16, 2022.

This is the result of the normal process of X inactivation, also known as dosage compensation or lyonization, that occurs randomly in female somatic cells[1]. To equalize expression of genes on the X chromosome among males and females, modifications of the chromosome packaging and DNA methylation patterns on one of the two X chromosomes in each female cell silences gene expression from that chromosome[1]. Selection of the maternally or paternally inherited chromosome for silencing occurs randomly in each female cell at an early phase of embryonic development, and the silencing of the selected chromosome is transmitted to each daughter cell[1]. As a result, females are mosaic for X-linked gene expression; some cells express the normal gene and some cells express the disease-causing variant. “Favorable” X inactivation (with a higher proportion of cells expressing the normal gene) may result in milder symptoms[1].

After stepping out of the room, you do a quick search on your phone for genetic forms of rickets. Based on the family history and the clinical history, you suspect either an autosomal dominant or X-linked form of hypophosphatemic rickets[2]. Based on the absence of male-to-male transmission, you consider that X-linked inheritance is still a possibility in this family. Since X-linked hypophosphatemic rickets is a dominant disorder and females have mosaicism of X-linked genes, this may explain why David’s mother appears to be mildly affected while her son has a more severe phenotype.

You present your findings and differential diagnosis to your preceptor. She is impressed that you have used the pertinent positives and negatives on history to present a prioritized differential! Great work!

That brings us to the end of the case for today! Let’s review some take-home points from this second episode in our 3-part series on Genetic Diseases.

1. X-linked inheritance occurs when a pathogenic variant is passed from generation-to-generation or appears as a new change in a gene on the X chromosome. This form of inheritance is characterized by absence of male-to-male transmission.
2. Females have two X chromosomes and all female somatic cells undergo a process of dosage compensation where most genes on one of the two X chromosomes are silenced to prevent over-expression of genes on the X chromosome.
3. Females who carry pathogenic alleles on the X chromosome may have variable expression of X-linked genetic diseases due to mosaic X chromosome inactivation.

Thanks so much for listening and don’t forget to listen to the final episode in this 3-part series on Genetic Diseases to learn about genetic testing technologies and the conclusion of David’s case!

<u>References:</u>

1. Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 8th ed. Philadelphia, PA: Elesvier; 2016.
2. Ruppe M. X-Linked Hypophosphatemia. In: Adam M, Ardringer H, Pagon R, Al E,

Developed by NAME and NAME for PedsCases.com.
October 16, 2022.

editors. GeneReviews®. 2012 Feb 9. Seattle, WA: University of Washington; p. 1993–2021.

Developed by NAME and NAME for PedsCases.com.
October 16, 2022.