Genetic Diseases 1: Autosomal dominant inheritance

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Introduction:

Hi, my name is Dr. Rozlyn Boutin and I am a 1st year resident at British Columbia's Chlidren's Hospital in Vancouver, BC, Canada. This podcast was developed together with Dr. Caitlin Chang, a medical geneticist at BC Children's. I would also like to thank Dr. Michelle Steinraths, a medical geneticist in Victoria, BC, Canada, for her assistance with developing this podcast. Today we will be discussing long QT syndrome as an example of a medical condition inherited in an autosomal dominant fashion. This is the first podcast in a 3-podcast series on Genetic Diseases. Don't worry if many of these terms are unfamiliar to you, we will start with a general overview of genetic principles and how various medical conditions can be passed down from generation to generation!

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

1. Define the role of a clinical geneticist in the patient care team.
2. Identify "red flags" for genetic conditions by taking a comprehensive family history.
3. Draw a family pedigree and use this to identify different modes of inheritance.
4. List 2 indications for genetic testing in family members of affected individuals.
5. Define the concepts of penetrance and variable expressivity.

Genetics play a role in virtually all diseases, and a basic understanding of genetic principles is therefore essential for all clinicians. Medical geneticists often receive referrals from Family Physicians in the community, as well as from specialists in areas ranging from Cardiology to Gastroenterology to Ophthalmology. Family Physicians and medical specialists also play a key role in identifying individuals at risk of having a genetic condition, as well as in helping to manage the care of patients with genetic conditions.

Let's begin with a case. Your preceptor asks you to see Louise, a 13-year-old female who has come to the clinic with her mother after fainting while chasing the ball during a soccer game. She has been referred to you by her family doctor, as he is concerned that Louise's presentation is not in keeping with a benign syncopal episode and is atypical for her age. Your preceptor asks you to get started with taking the patient history. As a medical student,

you are likely already aware of the importance of gathering a thorough clinical history as a first step in patient care.

You introduce yourself to Louise and her mother and begin taking Louise's history. You learn that Louise was born at 38 weeks gestational age via spontaneous vaginal delivery to a G2P1 mother. The pregnancy and neonatal course were uncomplicated. Louise is developmentally normal and has never required hospitalization or surgery. She recently started to play soccer in school and had her first game of the season last week, when she experienced an episode of fainting while sprinting after the ball. She doesn't remember having any chest pain or trauma right before the incident and felt well when she woke up.

You recall that in Medical Genetics, taking a thorough family history in particular is essential and remains the gold standard for assessing a patient's risk of having a genetic disorder. A family history can be used to create a graphical representation of a family tree in what is known as a pedigree, which can often reveal a particular pattern of inheritance of a genetic condition within a family[1,2]. Information about how a genetic condition is transmitted from generation to generation within a family can then be used to identify family members who may benefit from genetic testing or help to inform diagnostic and therapeutic strategies for affected patients. As you take the family history, you begin to sketch out the family pedigree.

You start by drawing a filled circle to represent Louise. In a pedigree, females are depicted as circles and males are depicted as squares[3]. Diamonds represent an unspecified sex. Affected individuals are symbolized by filled symbols, and the proband, or affected individual who first presents seeking care, is indicated with an arrow[3]. Horizontal lines are used to represent a marriage or union, and vertical lines link these unions with resulting offspring[3]. Individuals within the same generation are placed along the same horizontal plane and two horizontal lines linking two symbols indicates that the couple has at least one ancestor in common and is therefore consanguineous[3]. In the case of autosomal recessive conditions where two copies of a mutant allele are required for disease expression, individuals with only one copy of a disease-associated allele are called carriers, and are represented by placing a dot in the center of the symbol[3]. A line through a symbol indicates that an individual is deceased. The standard in Medical Genetics is to obtain at least a three-generation family history. We have included a link in the script for the podcast to a template available online with basic pedigree symbols so that you can follow along!

https://geneticseducation.ca/wp-content/uploads/2013/03/Family-history-tool-GECKO-Aug-2015.pdf

On family history, you learn that Louise's older brother drowned when he was 18 years of age and would faint during fire drills in school. Her maternal uncle died suddenly at 24 years of age but Louise's mother is unsure of the cause. Louise's mother was recently hospitalized for appendicitis and it was noted on her ECG that she had borderline long QT. Louise's maternal grandmother is healthy, but her grandfather passed away at the age of 65 from a stroke. He had a history of frequent syncopal episodes as a child and was disqualified from working as a paramedic as he was found to have something wrong with his heart during the physical exam required as part of the job application. He didn't like to

discuss this, so the family is unsure of what the specific problem was. Louise's parents are separated and she is no longer in contact with her father, but as far as she and her mother know, Louise's father and his parents are healthy. Louise's mother's side of the family is originally from England, and her father's parents are originally from France.

Before reviewing this with your preceptor, you quickly refresh your memory regarding genetics and patterns of inheritance. As you probably know, the human genome contains all of the information required for life in the form of DNA. Within the nucleus of every human cell, the genome is packaged into 23 pairs of chromosomes, including 22 autosomes, which are the numbered chromosomes, and one pair of sex chromosomes[1]. Half of an individual's chromosomes are maternally derived and inherited from the egg, and half are paternally derived from the sperm that fertilizes the egg to form a single-celled zygote with 46 chromosomes[1]. Males and females have the same set of autosomes, but sex chromosomes come in two forms, X and Y, and determine the biological sex of the offspring[1]. Males have one Y and one X chromosome, whereas females have two X chromosomes[1]. To help you visualize this, it is helpful to think of the genome as a bookshelf of books where each chromosome is represented by an individual book on the bookshelf. Within each book are letters that can be put together to make understandable words and sentences, just like how each chromosome contains many individual genes that each encode the blueprint for making a specific protein. These proteins, in turn, are what execute different tasks in the human body. Spelling mistakes in a gene, referred to as gene variants, can result in disease by altering the function of the encoded protein.

Diseases caused by disease-causing gene variants, or pathogenic alleles, at a single location in the genome are referred to as single-gene disorders[1]. These are typically categorized according to predictable patterns of mendelian inheritance[1]. Patterns of inheritance, in turn, are defined according to the type of chromosome the pathogenic allele can be found on and whether one or two copies of the allele are required for disease expression. The most common patterns of mendelian inheritance are autosomal dominant, autosomal recessive, and X-linked inheritance[1]. Autosomal dominant conditions arise when a single pathogenic allele on one copy of the 22 autosomes, or non-sex chromosomes, in the genome is required for phenotypic, or observable, disease expression[1]. On the other hand, autosomal recessive conditions require two copies of the pathogenic allele, one from each parent, to be present in the genome for disease features to be present[1]. Finally, X-linked inheritance occurs when pathogenic alleles are found on the X chromosome[1]. Individuals with a single copy of a pathogenic or mutant allele are referred to as heterozygotes, whereas those with two copies of a mutant allele are homozygotes[1].

Based on Louise's family history and the pedigree you have drawn, you take a moment to reflect on what pattern of inheritance might be involved. You note in your pedigree that males and females appear to both be equally affected, and that there are affected individuals in each generation. These features suggest a pattern of autosomal dominant inheritance. While not evident in Louise's pedigree, you can also look for male-to-male transmission to reassure yourself that a trait is not X-linked.

As you finish taking the family history, your preceptor calls you back into her office to discuss the case before you go back together to perform a physical exam and present the plan. You present the family history to your preceptor and she commends you for your thorough history-taking skills and accurate pedigree drawing! She points out that there are certain key features of a family history that can be considered 'red flags' suggestive of a genetic condition within a family[1,2,4]. Some of these red flags include:

1. Multiple family members affected.
2. Atypical presentation-ex. early age of onset relative to general population or present in less commonly affected sex.
3. Presence of disease in absence of other disease risk factors.
4. High-risk ethnicity.
5. Consanguinity.
6. History of congenital abnormalities.
7. Family history of stillbirths, infertility, serial unexplained miscarriages, or childhood deaths.

Your preceptor asks you to review your history to see which of these red flags are present in Louise's case, and which ones are suspicious for a heritable cardiac disorder in particular. Specific red flags you identify on Louise's personal and family history include syncope triggered by physical exertion and auditory stimuli in Louise and her brother, unexplained sudden death in an otherwise healthy young person in Louise's uncle and brother, and prolonged QT in her mother. Her grandfather may have had a long QT interval.

On discussion with your preceptor, based on Louise's presentation and her family history, you are suspicious of a diagnosis of long QT syndrome, a condition with autosomal dominant inheritance[1,4,5]. An EKG is ordered for Louise and demonstrates that her corrected QT interval is increased.

Your preceptor asks you what types of genetic investigations you can do to confirm the diagnosis. Are there any other tests or investigations you would like to do?

In order to help answer this, you review your teaching notes on long QT syndrome. Long QT syndrome is a term that encompasses a number of disorders, known as channelopathies, involving abnormal ion channels in cardiac cells[1,4,5]. Changes in the cardiac cell ion channels results in altered movement of ions across the cell membrane during cellular action potential propagation and result in prolonged ventricular repolarization[1,4,5]. As a result, the QT interval on an EKG is prolonged. As the QT interval gets longer, there is an increased risk of developing a dangerous heart rhythm known as *torsades de pointes*, which can lead to ventricular fibrillation and cardiac arrest[1,4,5]. Long QT syndrome often initially manifests as episodes of syncope, seizures, or sudden death, and is a common cause of sudden death in young, otherwise healthy people[1,4,5]. As many as 1 in 2500 people are affected with long QT syndrome, and the disorder is typically diagnosed based on personal and family history in conjunction with an EKG[1,4,5]. While an EKG is not sensitive or specific for hereditary long QT syndrome, this diagnosis should be suspected in

males with a QT interval of >450ms after correcting for heart rate and females with a corrected QT interval >470ms[1,4,5].

Importantly for our case, most cases of long QT syndrome are related to an underlying genetic abnormality inherited in an autosomal dominant fashion[1,4,5]. As many as 15 genes have been implicated in the disorder, but over 90% of cases have been linked to three genes referred to as *LQT1*, *LQT2*, and *LQT3*[1,4-6]. The most common form of genetic testing done to confirm a diagnosis of hereditary long QT syndrome is a gene panel. This type of test uses next-generation sequencing to assess the patient DNA sequence of genes associated with long QT syndrome. The sequences in the sample are then compared to the reference human genome to look for disease-causing variants. This information can be used in combination with a patient's history to help predict the risk of cardiac events.

So what is the benefit of confirming a diagnosis and performing genetic testing? Happily, long QT syndrome is treatable, and early cardiac death can be prevented.

As a keen medical student, you do your best to formulate a plan for Louise. How would you manage her long QT syndrome? As you do some reading on the topic, you learn that genetic testing can be used to help direct treatment[1,4-6]. For instance, beta blockers are known to be effective at preventing cardiac events in patients with LQT1, but are less effective in certain other subtypes of long QT syndrome[1,4,5]. Louise should avoid QT-prolonging medications, such as certain antifungals and over-the-counter cold medications (https://www.crediblemeds.org/), activities associated with intense emotion or stress, competitive sports, and electrolyte imbalances[1,4,5]. All patients with long QT syndrome should be referred to a cardiac arrhythmia specialist for further assessment, and further options for management may include inserting an implantable cardioverter defibrillator or pacemaker[1,4,5]. Finally, when Louise is starting to think about having a family in the future, she should be referred to a medical geneticist or counsellor to discuss the risks of passing the long QT-associated gene on to her offspring[1,4,5].

Great job! You have used your knowledge of basic genetic principles to work through this case. But what about the question of other tests or investigations? You think back to your pedigree and wonder if anyone in Louise's family should have genetic testing done. Your preceptor is impressed that you have thought about this and explains that testing of family members of affected individuals, known as cascade testing, can be an issue that carries a number of ethical dilemmas. Testing of family members is only indicated in certain scenarios. For example, testing in asymptomatic individuals for a disease that cannot be treated can cause significant anxiety, without any medical benefit. The risks of false-positive and false-negative results must also be considered.

Your preceptor mentions that for certain conditions, carrying a particular genetic variant does not necessarily mean that an individual will show signs of disease, and that in many cases knowing the particular genetic variant cannot be used to predict disease severity. Penetrance is a term used to describe the proportion of individuals with a disease-causing genetic change who demonstrate at least some degree of clinical features as a result[1]. For example, 25% of people with an identified long QT gene variant have a normal corrected

QT interval on baseline EKG[1,4,5]. Expressivity is a term that describes the severity of expression of a disease phenotype in individuals with a genotype associated with disease[1]. In the case of long QT syndrome, there can be variable expressivity within families. For this reason, if a baseline EKG is normal, an exercise EKG can be done to increase testing sensitivity[1,4,5].

In the case of long QT syndrome, all first-degree relatives of individuals with clinically diagnosed long QT syndrome or a known mutation in a long QT syndrome gene should be referred to a cardiac arrhythmia specialist and medical geneticist[1,4,5]. This is because the disease is treatable and can be clinically silent until a catastrophic event occurs. You make sure to discuss this with Louise and her mother. After your discussion, Louise's mother arranges to have genetic testing done for herself through your clinic. She is very grateful to you for all of your help, and for taking the time to explain everything to her so clearly!

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

1. Medical genetics play an important role in all areas of medicine, and an understanding of basic genetic principles is important for patient education and referral of at-risk patients with preventable diseases.
2. Taking a detailed family history is a key part of a medical genetics consult, and there are certain "red flags" you should watch out for that suggest a hereditary genetic condition within a family.
3. Genetic testing is recommended for family members of affected individuals in cases where results may change management and/or change clinical outcomes for the person being tested. Genetic testing results can also be used to counsel families regarding risk of passing on a disease-associated gene variant to their offspring.
4. Penetrance and expressivity are important genetic concepts that are important to consider when evaluating patients and thinking about testing relatives of affected individuals.

Thanks so much for listening and don't forget to listen to the other episodes in this series on Genetic Diseases to learn more about genetic testing technologies!

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