Katie

So I don't really remember being diagnosed because that happened the day that I was born. The story goes that my parents got told by the doctor that they'd seen a swollen right foot on their new baby and they wanted to check that out. So it's basically always been something that I knew was a part of my life, that I understood was part of who I was. It didn't really register that not everybody spent that much time sitting in hospital waiting rooms or being weighed and measured. It didn't really mean very much to me other than just that was what life was like, of course you go in and you get checked out for various things. As I got a bit bigger I understood that it was genetic and I kind of understood what that meant. But explaining that to other people was the bigger problem. I always wanted to try and explain it to other kids but they for some reason just didn't have as much interest in what a gene was as I did. And that became clear as I got older that that was a bit weird.

I missed quite a lot of school comparatively. In retrospect I'm pretty sure it was very annoying for my family to have to schedule around various medical appointments. But again, it was just something that happened, like of course you go in and get your blood taken and you go and get scanned for various things. That was just the thing that always happened. But it was sometimes hard not to be a little bit self conscious. I have one foot that's very swollen and I felt quite aware of that and self conscious of that. But other people sometimes didn't even really notice to be honest, I sort of figured that out as I went along. And my elbows don't go straight, they go off at an angle and nobody knows that at all unless I deliberately point it out to them. So what scandal were there, exactly? I think it was mostly heart and kidneys, those are the big ones, and lots of hearing tests, my hearing is a bit dodgy.

But the biggest thing was always about my growth pattern. Every time I went in as a child I would get up next to a measuring tape on the wall and the doctor would try and pull my head up a little bit to try and get a little bit of extra height out of me, make sure that I was standing up straight to the point where I occasionally had to yell that my feet were coming off the floor. Actually one of the stranger things was that I would get my growth chart and I could see that on the Turner Syndrome growth chart, I was right at the top. I'm absolutely top 1%, a giant among Turner people. But then they do the same plot on a regular people graph and suddenly I'm right down the bottom. I understood from that very early that my comparisons of looking around the Turner Syndrome clinic waiting room where I'm very tall and almost everybody is shorter than me was very strange.

Part of the reason for that is that as a child I had growth hormone injections, so those are ones that you do every day. I think that started when I was about 8 or 9, when I first started becoming notably smaller than my compatriots in my class at school. Initially my dad tried to do them for me while I was asleep but apparently that didn't work very well and I was a complete brat about it. They have a lot of special kits that they use to try and make it more comfortable for children, especially people who aren't very keen on needles which I wasn't at that age. So they're sort of strange injector pens and the one I had was almost like a gun, it was on a spring and it made a huge noise whenever I pressed it. So that actually freaked me out more than just doing it myself.

So eventually after a lot of annoying this, I ended up doing my own injections which was a sort of single injection every day. And that was actually fine, I don't really mind that so much in the end, it was more the logistics of it that were really irritating. So if ever you went away then you had to take all your medication with you in a cooler bag and then put it in the fridge. There was always a lot of staring when I had to go and put medication in the fridge if I went on school trips as a child. I remember going on one where I think we're in the lake district somewhere and me having to do my injection at the end of the day, some of the kids were staring around the door as I was trying to do it. That was not great.When I got a bit older the doctors started becoming very concerned about giving me what they called the normal experience of puberty. So they put me on HRT, hormone replacement therapy, a kind which includes giving you periods which I could really have done without, nobody needs that.

	But it was always in retrospect quite strange that nobody ever talked about that as an identity issue or even referred to it as an intersex condition. I actually had to figure that out as an adult. Nobody said those words. It was quite strange in retrospect, especially because they were always very clear that I wouldn't have my own children, that that just simply wasn't a physical possibility for me. And you would have thought that there would be a little bit more about that but apparently not. Then again I guess it affects so many different potential things that it's quite difficult to explain that to children. And I do now as an adult really appreciate that. So now my adult life is kind of well how many other things can it affect? Is this another thing that I need to worry about or do I need to get that checked out or do I need to consider this other thing?
	So currently I get scans of my heart and my kidneys regularly but also bone scans because along with the lack of natural estrogen is problems with your bone density and due to some other medical issues I had to stop the HRT. I just recently had a bit of concern that my parathyroid gland wasn't working right, although apparently it's actually fine because I didn't know what a parathyroid gland was until then. And the other biggest things at the moment I guess are getting shoes that fit, one foot and ankle is notably bigger than the other so that's a bit of a pain though I'm very lucky and I can usually just about manage a pair that are officially the same size. But I do have to wear a support stocking which is a sort of pressure sock and that is a pain, especially when it's really hot. Because if I don't do that then my ankle starts to swell up and my foot swells up and it also sort of aches. So I do wear my sock.
	I guess I'm almost certainly going to need a hearing aid at some point or another. If you go around a Turner Syndrome convention or a Turner Syndrome clinic waiting room, you will see lots of people with hearing aids and I've sort of I guess accepted that. I guess that's most of my story. It's a strange one to think that your life is a story because it really is absolutely everything to do with with who I am and how I live. I don't know what it would be like to not have that and trying to explain that is a bit strange but I hope that was helpful. There you go. That's the end of my story.
TPWKY	(This Podcast Will Kill You intro)
Erin Welsh	Thank you so, so much Katie for taking the time to chat and for sharing your story with us and with everyone.
Erin Allmann Updyke	Yeah, thank you. We really appreciate it.
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're talking about Turner Syndrome.
Erin Welsh	We are. I believe that it's not our first genetic foray.
Erin Allmann Updyke	Nope.
Erin Welsh	But I think it is of this season and it's definitely our first chromosomal one.

Erin Allmann Updyke	Oh yeah, that's a good point. We've only done single genes.
Erin Welsh	I think so.
Erin Allmann Updyke	I think, right?
Erin Welsh	I think so.
Erin Allmann Updyke	It's almost like we should keep a list or something, Erin.
Erin Welsh	Yeah, this is going to be a very interesting one. I don't know really anything at all about the biology and so I can't wait to ask you 1000 genetics questions.
Erin Allmann Updyke	Oh gosh, I can't wait to be like I don't know the answer. But I'll try. So maybe before we do that I think it's quarantini time.
Erin Welsh	I think it is. What are we drinking this week?
Erin Allmann Updyke	We're drinking Nothin' But Nettie. And I love that I don't actually know what that means yet because I know it's about a researcher but I haven't gotten to hear about her yet.
Erin Welsh	Well you will definitely get to hear about her. We named our drink after Nettie Stevens who was not as involved in Turner Syndrome research but was involved in uncovering what the X and Y chromosomes do.
Erin Allmann Updyke	Ooh.
Erin Welsh	And also her story is so interesting and so inspirational and so we just kind of wanted to pay tribute to Nettie.
Erin Allmann Updyke	Love it. And what is in Nothin' But Nettie?
Erin Welsh	In Nothin' But Nettie is gin, basil, some lemon, and cucumber. It's very refreshing and delicious.
Erin Allmann Updyke	I love it. Sounds phenom. We'll post the full recipe for Nothin' But Nettie as well as our non alcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	We sure will. On our website you can find a whole lot of stuff, we're not going to go through everything again. But I also just want to say real quick because we've not been mentioning it that we are always happy to receive firsthands. So if you are interested in sharing one of your stories on the podcast, please reach out to us, preferably either through the contact form on our website or by emailing us directly at thispodcastwillkillyou@gmail.com.
Erin Allmann Updyke	Well Erin, should we get started on the biology of Turner Syndrome?
Erin Welsh	Let's do it right after this break.
TPWKY	(transition theme)

Erin Allmann Updyke	So Turner Syndrome. Like we said at the top, this is a genetic condition and in this case Turner Syndrome is a condition that results from the partial or complete loss of one X chromosome. So before I get into any of what that means, I want to first set up some definitions of things that listeners probably are familiar with, at least from our high school biology classes, but that might have been a long time. So we'll go over it, shall we? So our X chromosome is one of our sex chromosomes. So what on earth is a sex chromosome? We'll start there. Essentially our chromosomes in general are conglomerations of our DNA and the proteins that our DNA wraps itself around.
	Humans, us, we have a total of 46 chromosomes and each of these are present in pairs. So we have 23 pairs of chromosomes. 22 of these pairs are what are called autosomes and one pair is our sex chromosomes. We get one of each of these pairs from our parents, one full set of 22 plus one sex chromosome from the egg and one full set of 22 plus one sex chromosome from a sperm. Those come together and ta-da! A zygote is formed. We can look at chromosomes in humans by looking at what's called a karyotype. And this is a way of taking DNA from our cells and literally laying it out so that you can see them. It's very cool, if you haven't seen images since high school bio we'll post them or you can google it also. And sex chromosomes in humans are our X and Y chromosome. They are called sex chromosomes because they in large part are responsible for the initiation of sex determination. What that means is that our X and Y chromosomes are those that contain genes that result in the formation of our gonads and other reproductive structures.
	Sex determination is then furthered along during development by the production of sex steroids like estrogen and testosterone which often come from our gonads. And then the development of secondary sexual characteristics. So in humans you can kind of think of it as a three step process of sex determination and sex chromosomes are integral to that first step of the process. And because they are then resulting in the formation of these gonads which produce sex steroids, they affect later stages as well. Cool? And everyone probably learned in high school biology that when it comes to sex chromosomes, XY equals male and XX equals female. And that might have been the last of what we all learned about sex chromosomes. So today we get to start the process in all of our brains of flipping that script because as we'll talk a lot about, it's not that simple.
Erin Welsh	It's not that simple.
Erin Allmann Updyke	It never is on this podcast.
Erin Welsh	It really is not.
Erin Allmann Updyke	So what is Turner Syndrome then? Turner Syndrome is what happens when an individual ends up with either an entirely or a partially missing X chromosome. And it turns out that when it's just a part of that X chromosome, it's often the tip of the short arm of the X chromosome, which as I'll talk about later is where many of the very important genes happen to sit.
Erin Welsh	That's very interesting. Okay, I have a question already.
Erin Allmann Updyke	Okay, shoot. Give it to me.
Erin Welsh	When it's completely missing, does there tend to be a pattern in whether it's missing from the sperm X or from the egg X?

Erin Allmann Updyke	Great question. I think from what I read it's more common that it's from the sperm X. So more commonly what you see is that the X chromosome that is present is from maternal DNA. So from the egg.
Erin Welsh	Interesting.
Erin Allmann Updyke	Yeah. And I don't think that we have a great idea as to why that is, at least not from what I read.
Erin Welsh	Okay.
Erin Allmann Updyke	And what's interesting too is that this can happen, both part of the X chromosome and an entire X chromosome being kind of left behind, during the process of meiosis which is formation of gametes, eggs and sperm. Or it can happen during mitosis. And what's very interesting is that Turner Syndrome can also happen due to something called mosaicism. And this is when a fetus that becomes a human has multiple cell lines in their body. And this happens when during very early cell division in a forming zygote there is abnormal mitosis that results to some cells having say only one X chromosome and some cells having two X chromosomes.
Erin Welsh	And so if you looked at the karyotype of this person, some cells would have to Xs and some cells would have XO or just one X.
Erin Allmann Updyke	Exactly. Yeah. So the way that they tend to write these when you are writing out the result of a karyotype is someone with complete monosomy of the X chromosome with Turner Syndrome would have the karyotype 45,X. Or 45,XO it's sometimes written. Someone who was a mosaic could have the karyotype 45,X in some of their cells and 46,XX or 46,XY in other cells.
Erin Welsh	Okay.
Erin Allmann Updyke	So already, how interesting.
Erin Welsh	Yeah. And so Turner Syndrome is not just one X, it's not just the mosaicism of two Xs in some cells, one X and other cells. It's also XY in some cells and X in others.
Erin Allmann Updyke	Yes, it absolutely can be.
Erin Welsh	Interesting.
Erin Allmann Updyke	Yes. And I'll get into a little bit more too about the intricacies that might arise when somebody might have that karyotype of 45,X and 46,XY. Because as it turns out it results in some different organ structure that can have different effects down the line. Ooh, we'll get there.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah. And those are not the only karyotypes that can exist. This again can be just from a partially missing or a structurally abnormal X chromosome. So you could have someone that is 46,XX but missing part of that X chromosome.
Erin Welsh	So really the crucial thing is that that part of the X chromosome is gone.

Erin Allmann Updyke	Yep.
Erin Welsh	Okay.
Erin Allmann Updyke	So there's a lot of possibilities there. Now before we dive too deep into what this looks like or what this results in, I also want to make a quick disclaimer especially for anyone who is going to go back and read some of the literature of Turner Syndrome. And that is that in a lot of the literature Turner Syndrome is characterized as a condition of women and girls. And this characterization isn't entirely accurate largely because gender is a social construct and it's not the same thing as sex which tends to be a biological characterization that is in large part, as I said, driven by genetics and particular sex chromosomes. So the characterization of Turner Syndrome as a condition of women and girls isn't accurate.
	On top of that, I think that what conditions like Turner Syndrome show us is that even this idea of sex as a binary of male and female isn't entirely accurate either. Our genetics are not nearly as black and white as what we learned in high school. And so some of the papers that I read referred to Turner Syndrome rather as a condition that affects phenotypic females, that is individuals who have especially at birth a phenotype, a set of observable often physical characteristics that make them be labeled as female. So just sort of throwing all that out there.
Erin Welsh	Yeah.
Erin Allmann Updyke	So what does Turner Syndrome look like or result in?
Erin Welsh	Yeah.
Erin Allmann Updyke	Unsurprisingly given the variety of genotypes and karyotypes that I just discussed, there is a large amount of variation in what the phenotype can actually be. And what that means is that there's also a lot of variation in what the downstream effects or potential medical conditions that might come along with Turner Syndrome are. And when you read back through a lot of the literature, especially as we get into what the epidemiology of Turner Syndrome really is, there's also an important distinction to be made between people who might have a particular karyotype, so a particular set of chromosomes, and whether people have any observable characteristics that are associated with Turner Syndrome. So in more modern definitions you have to have both the karyotype where you are missing part or all of an X chromosome in at least some proportion of your cells as well as a couple in particular of characteristics that go along with Turner Syndrome to actually meet the definition of Turner Syndrome.
Erin Welsh	Okay. So the number of individuals that might be missing that portion of the X could be higher than the number of individuals that are diagnosed with Turner Syndrome.
Erin Allmann Updyke	Absolutely, yes.
Erin Welsh	Okay. Do we know what that difference is?
Erin Allmann Updyke	It's a great question. I'll talk more about it in the current events section. The short answer is not really, no.
Erin Welsh	Yeah okay. That make sense.

Erin Allmann Updyke	Yeah. But we'll get there. But first let's talk about what are those characteristics to add to this karyotype to then result in this diagnosis of Turner Syndrome. The two main things that we see are short stature and gonadal insufficiency. So that means generally what's called primary amenorrhea, so not ever starting menses or sometimes initiation of menses that then over a couple of years stops and results in what's called secondary amenorrhea, so no longer having periods after just a couple years. There are a lot of other things that can go along with this like congenital heart defects and other heart conditions, kidney abnormalities, and a whole bunch of other things. And instead of just listing what they all are what I want to do is kind of focus on those two in particular most common characteristics, the short stature and the gonadal insufficiency, what we know about why we see those characteristics as it relates to this missing X chromosome, and then in that process we'll see what a lot of these other characteristic findings might be. Does that sound good?
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay. Spoiler, we don't have all the answers to this, like by a long shot. But the overall basis for a lot of the phenotypic characteristics as well as some of the medical conditions that can arise with Turner Syndrome is something called haploinsufficiency. What a great word. It basically just means there's not enough gene product being produced to preserve normal function.
Erin Welsh	Okay.
Erin Allmann Updyke	So we talked in some of our other genetics episodes like cystic fibrosis and sickle cell anemia about this idea of recessive genetic disorders, like you need two copies of an abnormal gene to actually have the disease because one copy that's normal gives you enough of whatever it is to not have disease. So this is like that same idea except kind of different because it's a whole chromosome.
Erin Welsh	It's like the same thing but kind of different.
Erin Allmann Updyke	You know, I feel like it's a decent enough analogy.
Erin Welsh	No, it is, it is. I'm with you.
Erin Allmann Updyke	But I guess it's that it's dominant. You really do need two copies of some of these genes to not have problems arise.
Erin Welsh	Yeah.
Erin Allmann Updyke	So here's where it gets even more interesting because we're dealing with sex chromosomes. In people who are 46,XX, they obviously have two X chromosomes which is twice as many as somebody who is 46,XY would have. And as it turns out the X chromosome is a gene rich chromosome that has over 1000 genes on it while the Y chromosome has less than 200. So what happens in the bodies of people who are 46,XX to prevent over expression, too much of these 1000 genes, is that one of the Xs is actually inactivated, it's turned off in the body cells, in the somatic cells but not the gonadal cells in the ovaries of people who have two copies of this X chromosome. This is a process that's called silencing or X inactivation. But 15%-25% of these 1000 genes are not in fact silenced.
Erin Welsh	Right.

Erin Allmann Updyke	And these genes are called escape genes because they escape inactivation or silencing. And these are the genes that we need and want to have two copies of in order to have enough gene product for normal function, in order to not have that haploinsufficiency. And do you know where else many of these genes are located?
Erin Welsh	On the Y I'm assuming?
Erin Allmann Updyke	On the Y chromosome! Isn't that so interesting?
Erin Welsh	This is really interesting.
Erin Allmann Updyke	So even though we don't necessarily know everything there is to know about the specific mechanisms of some of what we see in Turner Syndrome, in general it's these specific genes, many of which are located on the tip of the short arm of the X chromosome, that part that's often missing in people with Turner Syndrome. It's these escaped genes that likely lead to many of the characteristics or conditions that we can see a rise in Turner Syndrome.
Erin Welsh	That's fascinating. Okay, so what are these genes?
Erin Allmann Updyke	Great question.
Erin Welsh	What do they do?
Erin Allmann Updyke	So glad you asked.
Erin Welsh	Yeah.
Erin Allmann Updyke	So out of all those genes, we actually have one that we know for sure that we have good evidence of the kind of exact effect that we see due to haploinsufficiency. That gene is called SHOX. And this is a gene that is normally not inactivated on the X chromosome, it is present on both X and Y chromosomes and it stands for Short stature Homeobox-containing gene on the X chromosome. SHOX.
Erin Welsh	SHOX.
Erin Allmann Updyke	So this particular gene, SHOX, is in a family of genes called homeobox genes which are really important genes, like a whole suite of them, that regulate really key developmental processes during embryogenesis, during the process of the formation of an eventual human. And in the case of SHOX, this gene is expressed during embryonic development in very specific tissues including on the first and second pharyngeal arches, who cares what that is. But what those structures develop into in the fetus are the maxilla which is the top part of your jaw and the mandible which is the bottom part of your jaw, as well as parts of your inner and outer and middle ear. It also is involved in muscles that are involved in chewing and hearing. This gene is involved in your soft palate and a whole host of other skeletal areas like in the legs, in the hands. So this is a big deal gene. And decreased expression of this one gene out of hundreds that are likely involved in particular is the most strongly and convincingly correlated with some of the characteristics that are often seen in Turner Syndrome. So we can talk about what some of those are.
Erin Welsh	Yeah.

Erin Allmann Updyke	They are things like developmental changes to the inner, middle, or outer ears that can lead to things like having ears that are low set, so lower on the cranium than is typical which can lead to things like chronic ear infections especially in childhood. Very commonly either that process or other variability in the structure of the ear leads to some degree of hearing loss in people with Turner Syndrome which can manifest in a lot of different ways, it's usually not complete deafness but varying degrees of different forms of hearing loss interestingly. We also sometimes see things like scoliosis as well as osteoporosis, though that one is multifactorial, and that's because of some of the effects of SHOX on the development of the skeleton as well as other variations in the growth of the feet or the ankles or the hands, many of which can be seen in Turner Syndrome.
Erin Welsh	It's so much, there's so many things.
Erin Allmann Updyke	I know, I know. There is also something that can be seen quite commonly in developing fetuses that have Turner Syndrome on ultrasound that's called a cystic hygroma. This is a collection of lymphatic fluid that often forms on the back of the neck and forms into this cyst. This process is likely due not only to SHOX but to potentially multiple genes that are related to lymphatic drainage. But in many cases this cyst that's seen during fetal development resolves and can leave behind a more webbed-shaped neck.
Erin Welsh	Okay.
Erin Allmann Updyke	So that's a feature that's associated with Turner Syndrome. It can also lead to a small mandible, so a slightly underdeveloped lower jaw or a narrow palate on the roof of the mouth which can sometimes lead to dental problems later in life. But probably the biggest and one of the singular defining features of Turner Syndrome that has been very strongly shown to be associated with insufficiency of this gene in particular is the short stature that we often see. In general people with Turner Syndrome reach average adult heights that are about 20 centimeters shorter than average when compared I should say to people who are 46,XX of their same ethnicity or race.
Erin Welsh	Okay.
Erin Allmann Updyke	And while there is obviously a very huge range of full adult height, individuals with Turner Syndrome often also show decreased growth trajectories, both during fetal development as well as early childhood. So they can kind of fall off what we call their growth curves. But height of course is something that is multifactorial, it's not determined by this one specific gene. So the other reason that people with Turner Syndrome often don't attain as great of a height as would be predicted, especially by their parental heights, is because of a lack of a pubertal growth spurt. Why do we see the lack of a pubertal growth spurt? Well that's because of the effects of Turner Syndrome on gonadal function. So let's get into that, shall we?
Erin Welsh	Yeah, I'm excited about this.

Erin Allmann Updyke	Me too. I love talking about gonads. So in the ovaries, X chromosomes are not turned off entirely. It's only in our somatic cells, it's not just certain genes in the ovaries, it's the entirety of the X chromosome, both of them are supposed to remain active. So if someone has part or all of their X chromosome missing, even if it's only in the gonads such as for example in the case of a mosaicism, then there's going to be haploinsufficiency of genes involved in the function of the ovaries. We don't know in particular necessarily which jeans these are because it could be any of them but what this leads to is the loss of oocytes or eggs in the ovaries at a much more rapid pace than is typical. And this in turn leads to changes in hormone secretions, specifically our sex steroids, because our ovaries are what is secreted those hormones that then talk to our brain which secretes more hormones to talk to various parts of our body to grow, especially during puberty. And also to do things like grow breasts, grow adult hair patterns, armpits, genitals, etc, and eventually begin ovulation and then menstruation in the case of ovaries. So we first of all don't see this pubertal growth spurt and most often we also don't see menarche or the beginning of menstruation.
Erin Welsh	Okay, so what about people who have a Y chromosome? How does this picture differ or how is it the same?
Erin Allmann Updyke	Great, great question. So it can get fairly complicated because there's a lot of potential ways that that karyotype can present where people might have part or all of a Y chromosome. But what can often happen especially if someone is a mosaic, that is say 45,X in some of their cells and 46,XY in other cells, often will not form true ovaries but will rather form testes that then remain in the abdominal cavity rather than ending up in a scrotum because there generally is no scrotum, there is phenotypically female genitals.
Erin Welsh	Okay, gotcha.
Erin Allmann Updyke	And one of the big risk factors with this in particular is that when testicles remain in the abdomen, they're at higher risk of developing into certain types of gonadal cancers.
Erin Welsh	Why is that?
Erin Allmann Updyke	I think in part has to do with temperature differences but I'll be honest, I don't fully know. It's very interesting.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	And that's true across the board if testes are retained in the abdomen, it's not specific to Turner Syndrome.
Erin Welsh	Okay, yeah. All right.
Erin Allmann Updyke	But in all of these cases when it comes to gonadal insufficiency, whether we're talking about ovaries that are not fully developed or we're talking about testes that might be retained or some combination thereof because that's also possible, one big potential consequence of this is infertility. And so then the need for assisted reproductive technologies if somebody decides that they want to try and get pregnant later on.
Erin Welsh	What would that consist of?
Erin Allmann Updyke	Usually IVF and possibly with donor oocytes.

Erin Welsh	Okay.
Erin Allmann Updyke	It all just depends on what an individual's phenotype is and how much ovarian reserve they have, if any.
Erin Welsh	Okay, gotcha.
Erin Allmann Updyke	Yeah. And I do want to emphasize that this is a condition that has a very wide spectrum of phenotype. So some people, about a third of people with Turner Syndrome, do initiate menstruation spontaneously but the majority of them do then enter this secondary amenorrhea at a much more rapid rate than is typical for menopause.
Erin Welsh	Okay. I have a question about the proportions of different karyotypes. So in terms of Turner Syndrome and people with Turner Syndrome, what proportion of them are 45,X? What proportion of them have some mosaicism? What proportion of them have a Y chromosome? What does that breakdown look like?
Erin Allmann Updyke	Yeah. Love that you asked. In general most papers that I read estimate 45%-50% of people with Turner Syndrome are 45,X, that's their karyotype. About 20%-30% of people have some kind of mosaicism, be that 45,X with 46,XX or XXY, 47,XXY, etc, etc. There's a lot of possibility there. And then the rest have some other type of structural abnormality of one of those X chromosomes.
Erin Welsh	Okay.
Erin Allmann Updyke	So huge variation.
Erin Welsh	Yeah.
Erin Allmann Updyke	But wait Erin, there's more. Now another very medically important condition that can arise as a result of Turner Syndrome, and I'll just preface saying we do not understand the exact gene underpinnings here, are a variety of congenital heart defects. And this can really range. One of the most common is what's called a bicuspid aortic valve, this is the valve between your left ventricle and your aorta. And all of your valves in your heart are pretty important but this one is very important.
Erin Welsh	Okay.
Erin Allmann Updyke	And it typically has three leaflets but in a bicuspid valve there's only two. That means that these two leaflets are under a lot more stress and that can lead to stiffness of these valves and then eventually insufficiency of this valve.
Erin Welsh	Okay.
Erin Allmann Updyke	Another condition that's even a little scarier is aortic root dilation which means the root, the first part of the aorta as it comes off of the heart, and as a reminder for all listeners, your aorta is what carries your blood to literally all the rest of your body, when this gets enlarged and this enlargement makes it weaker. And this can then put you at risk for not only that aortic insufficiency where not enough blood is making it into your aorta to give blood to your body but it also can put you at risk for aortic dissection which is where the wall of the aorta comes apart and that can be life threatening.

Erin Welsh	Yeah.
Erin Allmann Updyke	Turner Syndrome can also be associated with other abnormalities like coarctation of the aorta which is where later on in the course the aorta kind of pinches in, gets more narrow, which can lead to increased pressure in some spots and decreased pressure and others. So you're not getting adequate blood flow to all of the body. And honestly there's a lot of other potential congenital heart defects that can result as well. There's a few candidate genes that might be involved and one paper that I read which of course I will link to really suggested that it's likely a two step process, where there's likely genes that are involved but then particular alleles that put you at higher risk for having these heart abnormalities.
Erin Welsh	That makes sense.
Erin Allmann Updyke	Yeah. So it's not just a haploinsufficiency issue. But yes, there's a lot of possibilities in terms of what the anomalies that we see in the heart can be and so we don't have exact answers as to the cause. And that is true when it comes to a number of other phenotypic characteristics or medical conditions that can be seen in people with Turner Syndrome. I can go through what some of them are but we really don't have as clear of an idea when it comes to these less common conditions or characteristics what the genes are that are involved or largely what kind of complex gene and hormonal interactions might lead to some of these.
Erin Welsh	It's so incredibly complicated.
Erin Allmann Updyke	It really, really is.
Erin Welsh	It boggles the mind, yeah.
Erin Allmann Updyke	So we can see things like kidney abnormalities and just like with heart anomalies, congenital heart anomalies, these can really range in terms of what kinds of structural kidney changes that we can see. People with Turner Syndrome often also tend to be at higher risk for autoimmune conditions, especially thyroid disease, but also inflammatory bowel disease and others. They tend to be at higher risk for hypertension. And there's some questions arising as to whether they are also at higher risk for diabetes. Seems clear that they are at higher risk for osteoporosis which is largely hormonally as well as gene regulated because estrogen is really important in healthy bone growth.
Erin Welsh	Right, yeah.
Erin Allmann Updyke	And in some cases individuals with Turner Syndrome can have difficulties in visual and spatial processing or visual motor tasks that can make some aspects of academics harder in some cases. But in general there's very we rarely any kind of global developmental delay or global learning disabilities or anything like that which is very interesting especially when it compares to many of the other aneuploidies or chromosomal genetic syndromes that we see. And I would say as well there's a paucity of data on the potential psychosocial effects of living with Turner Syndrome.
Erin Welsh	I'm sure the research has really only just begun.
Erin Allmann Updyke	It barely exists.
Erin Welsh	Okay, so I have a couple questions about treatment. Number one, gene therapy. Does it exist?

Erin Allmann Updyke	Great question. I saw nothing in my research about gene therapy. My guess is that it's largely because the SHOX gene is the only one that we have pretty decent evidence of its effect, whereas all of the rest of them were like yes, we know that these like escape genes are potential targets, but we don't even know what they do yet.
Erin Welsh	Right.
Erin Allmann Updyke	Yeah.
Erin Welsh	We don't want to just like throw a bunch in there and be like maybe this is okay.
Erin Allmann Updyke	Right, exactly.
Erin Welsh	Okay. So then my other question is treatment in terms of timing. So a lot of the things you described happen during development while you're a fetus, while you're an embryo, while you're a fetus.
Erin Allmann Updyke	Yeah.
Erin Welsh	But not everything. And so how does treatment play into that?
Erin Allmann Updyke	Such a great question. So when it comes to the things that might happen during development like say cardiac anomalies, congenital heart anomalies. As of now in general we don't have much in the way of treatments. There may be some very rare times where people get heart surgeries in utero but that's very, very rare, right. So in general the way that Turner Syndrome is dealt with in terms of treatment is twofold. There's two aspects of it that are often addressed during development if Turner Syndrome is diagnosed early enough and that is the growth insufficiency, so short stature, as well as the gonadal insufficiency. And those are treated with initiation of growth hormone and then eventually addition of estrogen therapy.
Erin Welsh	Okay.
Erin Allmann Updyke	Now the timing of those, very controversial. There are some societies that have guidelines but from what I read we just don't have a ton of evidence as to when really is the best time to initiate growth hormone and then add in estrogen, etc.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. But those are the two things. Growth hormone has been shown to increase final adult height substantially and the addition of estrogen reduces the risk of osteoporosis and can facilitate the growth of secondary sexual characteristics and importantly does not seem to increase the risk of any cancers which is always something to think about when it comes to estrogen.
Erin Welsh	Right, yeah.
Erin Allmann Updyke	Now the other thing that then we have to consider is the treatment of all of the other things that might go along with Turner Syndrome. And for those it generally just comes down to whatever typical medical management of those would be.
Erin Welsh	Right.

Erin Allmann Updyke	So if you have high blood pressure, you treat it like high blood pressure. But yeah, that's pretty much I think hopefully the biology of Turner Syndrome.
Erin Welsh	There's a lot there.
Erin Allmann Updyke	There really, really is Erin. So I gotta know how did we find out about this? How did we figure out that this was a condition when it can have such varied appearance and then how did we figure out what we know about it?
Erin Welsh	Good questions, good questions. I will do my best right after this break.
TPWKY	(transition theme)
Erin Welsh	At its core the history of Turner Syndrome is a story of chromosomes, specifically the X chromosome. I mean of course there's more to it than that, there is Dr. Henry Turner, the Oklahoma physician that in 1938 first described some characteristics that were associated with the condition, there's the improvements in our understanding of genetics that allowed researchers to pinpoint the chromosomal cause in 1959, and there's the founding and growth of many Turner Syndrome organizations over the past 50 or so years that have done so very much in terms of education, access to treatment, and connecting affected individuals and families all over the world. But what I really want to dive into today is what came before all that, the story of this chromosome at the heart of Turner Syndrome.
Erin Allmann Updyke	Yeah.
Erin Welsh	The X chromosome, like you said Erin, is one half of the pair of chromosomes, the other being Y, that we usually refer to as the sex chromosomes because they're involved in the process that ultimately leads to the formation of sexual organs and other sexual characteristics. They're not the only things involved of course nor is sex determination the only thing they do, as we know. So how did we come to call these two chromosomes sex chromosomes?
Erin Allmann Updyke	Ooh, I don't know.
Erin Welsh	How did the growing field of genetics uncover their functions and how has our understanding of sex chromosomes changed since then? I want to dive into these questions about the history of sex chromosomes and then I'll talk a bit about how Turner Syndrome was first discovered. People have always been obsessed with explaining why some people are born with testes and others are born with ovaries and all of the variation in between. And in the century leading up to the discovery of the X and Y chromosome, things like heat, the position of the fetus in the womb, and the types of food you ate were all contenders for what sex the infant would have, what phenotypic sex the infant would have. There are countless other beliefs or explanations that emerged over the thousands of years since humans first thought to wonder about anatomical differences and the vast majority of these explanations tended to suggest that it was kind of these more external factors after conception that made all the difference.

	Sex was pliable, it could be influenced by things after conception. But humans only began to get a peek at the complex internal processes that go into determining what we call biological sex at the end of the 19th century, beginning of the 20th, when the X and Y chromosomes were first discovered. And even then it would take a bit of time before this explanation of chromosomal sex determination was widely accepted. This was the end of the Victorian Era which was a period marked by strict gender roles, both privately and publicly, and so it may be kind of surprising to learn that during that same time scientists studying sex saw it as a spectrum, as extremely complicated and not necessarily a discrete binary trait.
	And this view is reflected in how these researchers thought sex was determined which was like I said largely through these sort of external factors affecting the embryo or fetus rather than something that was determined at fertilization. For instance, did the egg come from the left or the right ovary? How old was each parent? What time of day did fertilization happen and what was the temperature? What did you eat? All of these things. And the research that many early embryologists and physiologists were doing at the end of the 19th century supported this notion that sex was highly flexible. Sex ratios of certain insects varied under certain environmental conditions and study of sex hormones in birds and rodents showed that sex or sex characteristics could be modified after fertilization occurred.
Erin Allmann Updyke	I love talking about sex in other animals.
Erin Welsh	I know, I think that we need to devote an episode to that somehow.
Erin Allmann Updyke	It would be so fun.
Erin Welsh	It would be so fun. And this idea that sex was a plastic, changeable trait influenced by both the internal and external environments led to the quote "metabolic theory of sex" put forth by Patrick Geddes and J. Arthur Thomson in their 1889 book 'The Evolution of Sex'. Essentially the idea was that females of a species should have a higher metabolic rate due to the increased demands of producing large gametes, eggs, while males of a species would have lower metabolic demands because their gametes, sperm, weren't as energetically costly to produce. And this fed into the concept that during times of scarcity more males would be produced, while during times of plenty more females would be. And that actually is at least in part what seems to happen in some species, I think insect species. Not what happens in humans necessarily as far as I think we have learned at this point in 2022.
	But the metabolic theory of sex predominated for a few decades from around when it was introduced in 1889 or so until the 1920s. What ended up dethroning it? Chromosomes. Before we get into the how and why of when chromosomes were recognized to be major players in sex determination, let's take a step back to get some broader context in what was going on in the world of genetics or evolutionary biology at this time. And this is fun because I don't think, like I've done a whole lot of context setting for germ theory and antibiotics and all the infectious disease stuff we cover but I don't think I've really done it as much for evolution.
Erin Allmann Updyke	I don't think so.
Erin Welsh	Yeah. Okay. Well if it's a repeat, apologies and I hope it's okay.
Erin Allmann Updyke	If it's a repeat, we don't remember so no one else does either.

Erin Welsh	Yeah. So as we know, the 19th century was a tremendous time of change and progress in really all fields of science. We've talked on this podcast in depth about things like physics, about things like the revolution that was germ theory, microscopes and medical measuring devices were changing the way that we saw both health and disease, and natural historians were traveling all over the world and returning home to fill the halls and basements of museums and their own private collections with specimens from every continent.
	One of these natural historians by the name of Charles Darwin came back with more than just an outrageous number of plants and animals. He also brought back with him an idea that would change the way we looked not just at ourselves but at all life on earth. His idea which took him a few years to write up and publish was the theory of evolution by natural selection. The individuals of a species that are more fit for their environment are more likely to survive and reproduce and their offspring will inherit those traits that made their parents more fit. In this way, species change over time in relation to their environment, all components of it.
	As you probably already know, this idea met with a lot of resistance when it was first introduced with critics calling it sacrilegious or just bad science but over the next few decades research uncovered more and more evidence in support of Darwin's idea and many scientists turned towards working out the details of how evolution actually happened rather than trying to disprove it. And one of the key questions that remained about the process of evolution was how the information got passed from parent to offspring. What was the information actually made of and where was it located? Fortunately microscope technology could step up to provide some tentative answers.
Erin Allmann Updyke	I love this.
Erin Welsh	Just like the intersection, the combining of these different these different fields.
Erin Allmann Updyke	Yeah. Love it.
Erin Welsh	So while Darwin was looking across each eons of change, other researchers were a bit more microscopically focused, literally. Around the same time that Darwin was writing and rewriting and editing and stressing out about 'On The Origin of Species' which was published in 1859, another biological theory was gaining traction, the cell theory, which basically stated that the basis of all life is cells. All living things are composed of cells, cells are the basic units of all living tissue, and all cells come from preexisting cells. Of course people had observed cells and used that name since around 1665 when Robert Hooke first used that word to describe the little boxes he saw in a piece of magnified cork, since they reminded him of the rooms that monks stayed in called cellula.
Erin Allmann Updyke	Oh my goodness.
Erin Welsh	So that's where cell comes from.
Erin Allmann Updyke	I don't think I ever knew that.

Erin Welsh	But over the next 200 years or so microscope technology had advanced to the point where people could not only look at cells in a tremendous variety of organisms and tissues but also within cells themselves, identifying different components, making inferences about their functions, and observing the variety of processes involved in day to day cellular activities. Processes including cellular division via mitosis or meiosis. Researchers observed that the cells produced via meiosis were germ cells, so these sperm and eggs, and they were different from those produced during mitosis. And I'll get into that in a second. And in the 1890s German physiologist August Weismann integrated Darwin's theory of evolution with cell theory, proposing that the recombination of the germ cells was how information from each parent was passed down to their offspring and that the recombination process introduced the variation that would allow for natural selection to act because there has to be variation for natural selection to act.
Erin Allmann Updyke	Oh my goodness. It's beautiful.
Erin Welsh	It's so beautiful. But still the question remained. Where is that information stored? Experiments in the 1880s demonstrated that it had to be in the nucleus. But in what form? How is it packaged? Chromosomes seemed a likely contender.
Erin Allmann Updyke	Okay.
Erin Welsh	While early cell biologists were hunched over their microscopes watching these cells go through this beautiful dance of division, one in particular, German psychologist Walther Flemming, noticed something happening in the nucleus. He wrote that he observed the separation and copying of quote "threads" in the nucleus during division. 10 years later those threads would be designated chromosomes by Heinrich Waldeyer because they stained so easily, you could visualize them very well with staining.
Erin Allmann Updyke	Wait, why does that mean chromosome?
Erin Welsh	Chromo.
Erin Allmann Updyke	Oh chromo!
Erin Welsh	Yeah.
Erin Allmann Updyke	Wow, I never got that.
Erin Welsh	I never thought about it, yeah.
Erin Allmann Updyke	Me neither.
Erin Welsh	Okay so chromosomes got the name because they were so easily stained.
Erin Allmann Updyke	I love it.

Erin Welsh	And it turns out that mitosis and meiosis acted differently on these chromosomes. So mitosis is when a cell divides to produce two identical daughter cells, each containing two full sets of chromosomes. While meiosis produces four granddaughter cells, each with only one set of chromosomes. And so it stood to reason that these chromosomes contained in the nucleus with only one set present in germ cells could contain that hereditary information. And crucially that information in the germ cells, those chromosomes, would be passed down to offspring without the changes that would accumulate in the somatic cells during an individual's lifetime, basically making it actual evolution as we know it rather than this Lamarckian passing down acquired traits during a lifetime type of thing.
Erin Allmann Updyke	Yeah, okay.
Erin Welsh	Okay. So it took some time for the role of chromosomes and genetics to be fully embraced but in the meantime plenty of researchers had turned their efforts to learning more about these mysterious threads and the things they do, including possibly sex determination. We're finally here.
Erin Allmann Updyke	We've come full circle.
Erin Welsh	I haven't even mentioned Turner Syndrome in this yet and it's still going to be a while.
Erin Allmann Updyke	It's so good though.
Erin Welsh	Okay. In 1891 a researcher named Hermann Henking observed a strange extra chromosome, question mark, in the sperm of the fire wasp. At least he thought it was a chromosome. He also thought it could be a quote "peculiar chromatin element" or the quote "X element". People debated what this X element might do but generally the consensus was dismissal. It was a degenerate was the word they used chromosome that was at the end of its evolutionary history and had little to no function. And for a few years that was the end of it.
	Until around 1902 when a PhD student at the University of Kansas named Clarence McClung found a quote "peculiar nuclear element" that he ended up calling the accessory chromosome in the sperm of some locusts. He commented on the similarity between what he found and what Henking had found and suggested that this was not some crumbling chromosome at the end of its life but rather a fully functional chromosome that played a role in determining sex, since he observed its presence in some sperm but its absence in others. Quote: "A careful consideration will suggest that nothing but sexual characters thus divide the members of a species into two well defined groups and we are logically forced to the conclusion that the peculiar chromosome has some bearing upon this arrangement."
Erin Allmann Updyke	Interesting.
Erin Welsh	At the time this was a very bold claim. Chromosomes were generally thought to be the heritable units in the germ cells and that each one was probably responsible for some traits but the metabolic theory of sex where sex was more pliable and could be changed after fertilization, that still predominated. McClung himself didn't really pursue the idea any further but other researchers certainly did. Two in particular would be instrumental in demonstrating that these accessory chromosomes played a role in sex determination and it seems like it's only recently really that one has gotten the credit she deserves. The same year that McClung published his hypothesis, 1902, Nettie M. Stevens, who was at Bryn Mawr College and Edmund Wilson at Columbia University, both began examining this accessory X chromosome, mostly using insects. I feel like insects were always being used. They're fascinating, there's just such variation.

Erin Allmann Updyke	Yeah. Plus they're so easy to raise.
Erin Welsh	Histories of the X chromosome or sex determination by chromosomes often credit Wilson or even Thomas Hunt Morgan who was also at Bryn Mawr with Stevens with making the connection between X and sex. While Nettie Stevens is included often as a footnote or maybe worse as just providing supporting evidence of Wilson's claims. But closer examination of the timeline of events shows that Stevens should not only be recognized for being the first to demonstrate chromosomal sex determination but also for her many other important contributions to the field of genetics, such as I don't know, discovering the Y chromosome.
Erin Allmann Updyke	Kind of a big deal.
Erin Welsh	Kind of a big deal. I think Nettie Stevens' story is fascinating and so I just want to talk a bit about it before getting back to this history of discovery.
Erin Allmann Updyke	I love it, can't wait.
Erin Welsh	Nettie Stevens was born in Vermont in 1861 and went to school to become a teacher which is what she did for a number of years. Somewhere along the way though, she became fascinated with biology. And so she saved up money from her teaching jobs to go to Stanford University.
Erin Allmann Updyke	Wow.
Erin Welsh	She was 35 when she enrolled and 38 when she graduated with her Bachelor's.
Erin Allmann Updyke	I love her already.
Erin Welsh	I know. I mean I'm 35, the thought of going back to school, it's difficult. It's really hard to get that motivation. Yeah. So it's amazing,
Erin Allmann Updyke	I imagine in the 1800s it would not have been easy either.
Erin Welsh	No, exactly. It's unbelievable. The next year she got her Master's also at Stanford and then went on to Bryn Mawr for her PhD which she got at the age of 41.
Erin Allmann Updyke	Wow.
Erin Welsh	That is so inspirational. So it was 1902 when that happened.
Erin Allmann Updyke	Wow.
Erin Welsh	At Bryn Mawr, first as a PhD student during which she published nine papers by the way and then as a researcher, Stevens became fascinated by the fields of embryology, genetics, and cytology. Her postdoctoral fellowship allowed her to pursue independent research at Bryn Mawr while not having to teach.
Erin Allmann Updyke	Wow.

Erin Welsh	And during that fellowship that she did the bulk of her groundbreaking work on sex chromosomes.
Erin Allmann Updyke	Okay.
Erin Welsh	Let me read to you part of the concluding paragraph of her 1905 paper where she presented her findings about the common meal worm and sex determination by chromosomes. Quote: "Since the somatic cells of the female contain 20 large chromosomes while those of the male contain 19 large ones and 1 small one, this seems to be a clear case of sex determination, not by an accessory chromosome but by a definite difference in the character of the elements of one pair of chromosomes of the spermatocytes of the first order, the spermatozoa which contain the small chromosome determining the male sex, while those that contain 10 chromosomes of equal size determine the female sex."
Erin Allmann Updyke	Right out. Just boom.
Erin Welsh	Done. Yep.
Erin Allmann Updyke	Yep.
Erin Welsh	So that was very strong supporting evidence. And around the same time Edmund Wilson also published results that mirrored the findings of Stevens but his conclusions about sex determination by chromosomes were undoubtedly influenced by her work. So one paper I went through traced the footnotes and the revision process of the paper and how the things that he changed after her paper came out, just all this stuff.
Erin Allmann Updyke	Oh how interesting.
Erin Welsh	This paper was great, yeah. And also his study system was one in which the male of the species has one fewer chromosome than the female. And so initially he was thinking it was more about dose rather than dominant recessive characteristics.
Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. And not to mention that even in that paper he said yeah, chromosomes probably play a role in sex but it's more about metabolism. I mean ultimately the question of who gets priority for a certain discovery is always a bit of a sticky one. And maybe it's more important not to say this person is first, no this person is first, but to take a closer look at why there is discrepancy or why one person is given credit over the other. And I think it's safe to say that in Nettie Stevens case her gender played a role. Despite her incredible accomplishments she was never given a faculty position and while her colleagues recognized her brilliance, quote, "Of the graduate students that I have had during the last 12 years, I have had no one that was as capable and independent in research work as Miss Stevens." That was in one letter of recommendation I think from Thomas Hunt Morgan.
Erin Allmann Updyke	You mean Dr. Stevens.
Erin Welsh	Dr. Stevens. Yeah, she's I'm pretty sure a doctor at that point. But a lot of these accolades, a lot of these this praise was almost always qualified by for a woman. Quote: "I consider her not only the best of the women investigators but one whose work will hold its own with that of any of the men of the same degree of advancement."

Erin Allmann Updyke	Tried but missed the mark.
Erin Welsh	Yeah. Yeah. I mean it sucks but that's the way it was.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I think it is really important to acknowledge that.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	But I don't know. Also in one paper I read about Nettie Stevens, the author pointed out that it was probably for the best that Thomas Hunt Morgan who was also at Bryn Mawr and a huge name in in genetics was initially so resistant to Stevens' ideas about the role of chromosomes in sex determination because if he had been more on board, his name would have been on all her papers and he probably would have gotten all the credit and her name would have been forgotten entirely.
Erin Allmann Updyke	Wow.
Erin Welsh	Interesting to think about.
Erin Allmann Updyke	Yeah.
Erin Welsh	Well and then I think there's the trend that happens where if someone is very highly accomplished in a number of different fields, they tend to be given credit for things even if they maybe didn't play the biggest role in it. In any case I just wanted to spend a bit of time on this brilliant scientist who made so many incredible accomplishments in the field of genetics in such a short amount of time and during a time when so many things were working against her. And she probably would have made many more if her life was not cut short sadly by breast cancer. She died at the age of 50, only 9 years after finishing her PhD.
Erin Allmann Updyke	Oh my goodness.
Erin Welsh	I know, I know.
Erin Allmann Updyke	Wow.
Erin Welsh	But the work by Stevens and Wilson greatly our understanding of how chromosomes are involved in sex determination. But it would take a number of years before that idea was widely accepted due in part to just how much variation there is across the animal kingdom. Geneticists looking for a universal answer as to what determines sex, such as XX produces females and XY produces males, were continually thwarted by exceptions to that narrow rule. Some bird, sea urchin, and insect species where females were XY or ZW and males were XX or ZZ or insect species where males were either XO or XY, I mean the variation in these systems kept researchers from concluding definitively that these chromosomes were involved in sex determination. And this is reflected by it taking until the 1920s for these chromosomes to be widely referred to as sex chromosomes.
Erin Allmann Updyke	Interesting.

Erin Welsh	Yeah. Up until then they were known by a variety of names including hetero chromosomes and accessory chromosomes, ideo chromosomes. Even when it became clear that sex determination was part of what these chromosomes did, some researchers rejected these labels partly because they weren't quite convinced that that was how it worked, partly because they felt that too much was still unknown about other processes of sex determination and the function of these chromosomes, and partly because they felt that it was too simplistic and didn't capture the full spectrum of sex. It turned sex into a binary and I'm going to come back to this aspect of sex and sex chromosomes in a bit but for now I want to turn briefly towards the actual topic of today's episode, Turner Syndrome. Or should I say Ullrich-Turner Syndrome.
Erin Allmann Updyke	Perhaps.
Erin Welsh	The first half of the 20th century saw continued interest in sex chromosomes and genetics as well as another rapidly growing field, that of endocrinology. So around the same time that people were debating what to call the X and Y chromosomes, other researchers were busy characterizing hormones, particularly the ones that seem to play a role in the development of secondary sexual characters. For example these hormones that that you mentioned Erin, estrogen and testosterone, right. Henry Turner, an Oklahoma physician, was one of these early endocrinologists and he would frequently be asked to consult on cases where people were suspected to have different hormone levels or a different hormone functionality. Throughout the 1930s he noticed in seven of his patients that were assigned female at birth what he thought might be a previously undescribed hormonal condition that led to a suite of physical characteristics including short stature, cubitus valgus is one thing that he pointed out, which is that that extra angling of the forearm at the elbow.
Erin Allmann Updyke	Yeah.
Erin Welsh	And underdevelopment of sexual organs and secondary sexual characteristics. And in 1938 he published case summaries of these seven individuals and suggested that this was a newly described condition that was likely caused by a hormonal imbalance. He tried pituitary growth hormones to no avail and anterior pituitary gonadotropic hormone to some avail. I don't know what that hormone actually was.
Erin Allmann Updyke	I don't know.
Erin Welsh	That was in the paper. Yeah. He was right that it was a condition with one specific cause which is what ultimately ended up making him the namesake of Turner Syndrome and that hormones were involved. But he was wrong about it never having been described before. Remember how I called it Ullrich-Turner Syndrome? You might have seen that places.
Erin Allmann Updyke	Sure did.
Erin Welsh	Yeah. Turns out a German pediatrician named Otto Ullrich had actually published a case study of an 8 year old with the same suite of characteristics that Turner had described but eight years before Turner's paper came out. With Ullrich and especially Turner's work, there was now a clinical description of this condition but the ultimate cause remained a mystery for a couple of decades. Was it hormones? Was it something else? How did this happen? And it was only in 1959 that genetic technology and imaging had advanced to the point where researchers Ford et al were able to link cases of Turner Syndrome with the presence of only one X.
Erin Allmann Updyke	Wow. That's a long time.

Erin Welsh	It's a long time. I mean it makes sense I guess in terms of technology and our understanding of chromosomes and how everything worked and being able to actually work with them.
Erin Allmann Updyke	Right, right. And karyotype enough people or individuals and things like that.
Erin Welsh	Yeah, exactly. Side note, remember the person that Ullrich described in his case report, the 8 year old?
Erin Allmann Updyke	Yeah.
Erin Welsh	So a couple of researchers followed up in the 1970s and confirmed just one X.
Erin Allmann Updyke	Wow, that's kind of cool.
Erin Welsh	Isn't that cool?
Erin Allmann Updyke	Yeah.
Erin Welsh	In the years since the 1959 paper showing that a single X was at the root of Turner Syndrome, we've learned so much more about it including the fact that it isn't always a whole X missing, right, you talked about Erin,
Erin Allmann Updyke	Yeah.
Erin Welsh	Which specific genes might be involved and what types of treatments seemed to be helpful. And right alongside that we've been expanding our view of sex overall. The X and Y for humans I think provides this enticingly simple binary picture of sex. XX means female, XY means male. But obviously there's much more to it than that and I think it's important to remember that there are so many different ways you can categorize sex and some categories might be discrete, others are continuous, and none are binary.
Erin Allmann Updyke	Yeah.
Erin Welsh	Chromosomal sex, gonadal sex, hormonal sex, genital sex, sexual identity to name just a few. The diversity of sex and humans alone is amazing and I didn't even talk about other animals. For instance like I mentioned earlier, instead of the XX, XY system that we're familiar with, some birds and other organisms have a ZZ, ZW system where ZZ develops as males, EW as female. There are also systems that don't just use this master switch on the distinct chromosome, like the SRY on the Y chromosome to kick off the sex determination process but also use genes on autosomes, the non sex chromosomes that are involved in this process.
Erin Allmann Updyke	Yeah. And then there's so many animals too that can switch sex during their lifetime, well after development.
Erin Welsh	Yeah.
Erin Allmann Updyke	Like what? What?
Erin Welsh	And for some environmental factors play a huge role.

Erin Allmann Updyke	Right.
Erin Welsh	Temperature, stuff like that.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's not ridiculous. The metabolic theory of sex works, it's just is there an overarching theory of sex and how sex determination works? I don't I think there is.
Erin Allmann Updyke	Yeah.
Erin Welsh	Does there need to be? Isn't that sort of the beauty of it all?
Erin Allmann Updyke	But it's fascinating.
Erin Welsh	I am going to link to some papers because don't you want to know more about species that have lost the Y chromosome entirely or those that have evolved to have another type of X?
Erin Allmann Updyke	Yep.
Erin Welsh	Read about the African pygmy mouse with an XYW system.
Erin Allmann Updyke	What? What? What?
Erin Welsh	I know. The variety in this is beautiful, it's breathtaking. And I'll link to a few papers on our website that go into these examples ao you can read more and get hyped also about the diversity of sex. I especially recommend Moore and Roberts from 2013 titled 'Polygenic Sex Determination'. It's a really well written, accessible, fascinating paper. And there's so much more that we could talk about in terms of sex and sex chromosomes but I have to stop somewhere because otherwise I will never stop ever. So what I want to do is I want to ask listeners to send in your favorite sex chromosome trivia and all the different animals and then hand it off to you, Erin. So tell me, where do we stand with Turner Syndrome today?
Erin Allmann Updyke	Oh I can't wait to. But also Erin, that's how we make our whole episode about sex chromosomes is we just share listener facts. I love it.
Erin Welsh	Actually I love that a lot.
Erin Allmann Updyke	But I'll get into what we know about Turner Syndrome today right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Most of the papers that I read cited relatively similar statistics which is interesting especially in the context as we'll learn that we don't know, these are estimates.
Erin Welsh	We never know.

Erin Allmann Updyke	We never know. That's the theme of this section. But in general the estimate is about 1 in 2000 phenotypically female live births result in Turner Syndrome. Another way to enumerate that although it's looking at the literature a little bit more problematic is that about 50-60 of every 100,000 adult, the literature says adult women have Turner Syndrome.
Erin Welsh	Okay.
Erin Allmann Updyke	Right. So rare but not that rare.
Erin Welsh	It's one of the most common if not the most common of sex chromosome anomalies, right?
Erin Allmann Updyke	Absolutely. 100% yes.
Erin Welsh	Okay.
Erin Allmann Updyke	Now we don't have information on what the variation is globally in different populations in different regions largely because we just don't have data for most of the world to be able to say these regions have higher or lower incidence of Turner Syndrome. But what's interesting about Turner Syndrome is looking at the time frame of diagnoses I think because there are three main peaks of when people are diagnosed. It can be diagnosed prenatally via genetic testing, amniocentesis, things like that. And so some percentage of people, and I don't have an exact number on this, are diagnosed very early, like before birth even potentially. And then there's usually a second peak of people being diagnosed not until young childhood when they fall off their growth curves. And then pediatricians are like let me think, look at these other characteristics, perhaps we should get a karyotype.
Erin Welsh	Okay.
Erin Allmann Updyke	And especially through adolescence when people perhaps have primary amenorrhea and present in teen years having no period and then get worked up. And then the last peak might not come until adulthood when someone might be diagnosed because they're struggling with infertility.
Erin Welsh	Interesting, okay.
Erin Allmann Updyke	And it's estimated that potentially up to 20% of people may never be diagnosed and the reason that this is important is because it kind of gets back to like what is the definition of Turner Syndrome?
Erin Welsh	Yeah.
Erin Allmann Updyke	Right. If you are never diagnosed with Turner Syndrome, do you have Turner Syndrome and are just undiagnosed or do you not actually have any of these phenotypic characteristics of Turner Syndrome, therefore you might have this karyotype but you don't actually have Turner Syndrome. And that's kind of, I don't know, a philosophical question.
Erin Welsh	Right. Well I think it's also a clinical question too.

Erin Allmann Updyke	It is a clinical question definitely. Where we get this 20% number is from some studies that have been done in Great Britain and a few other countries that have looked at karyotypes of people across the board and found a much higher prevalence of Turner Syndrome than would be expected. So underdiagnosis essentially. Now another thing that I think is important to note because it's really fascinating and gets to a lot of what you were talking about, Erin, on just how interesting sex chromosomes are is that it's actually very rare to be born with Turner Syndrome, especially with a 45,X karyotype. So those numbers that I just cited, 1 in 2500, not that rare.
Erin Welsh	Right.
Erin Allmann Updyke	And 45%-50% of those people are 45,X. But it's estimated that up to 99% of fetuses with a karyotype of 45,X actually result in spontaneous abortion, ie miscarriage or early pregnancy loss.
Erin Welsh	That's very interesting because yeah, you're right, it's common but also extremely rare.
Erin Allmann Updyke	Right. And it's also important to note because, fascinating, that I am fairly positive that Turner Syndrome especially as 45,X is the only known survivable monosomy where you have a complete absence of one chromosome. The complete absence of any of the other sets of chromosomes results in a non viable fetus.
Erin Welsh	Wow.
Erin Allmann Updyke	There are partial monosomies like Cri du Chat, there's 17q12 microdeletions, there's other types of chromosomal anomalies and of course there are various trisomies, a number of which are compatible with life. But 45,XO is the only one with an entirely missing chromosome that's compatible with life which is pretty incredible. And there is actually some suggestion that perhaps those fetuses that do survive might have some some degree of mosaicism that we're just not detecting. But so far there's not a lot of evidence to actually confirm that hypothesis.
Erin Welsh	Right.
Erin Allmann Updyke	So suffice to say there are a lot of areas that are ripe for research, so many. There are a few really great papers that I will direct to that have a lot more detail on kind of what especially the medical community thinks are the greatest needs when it comes to research on Turner Syndrome. But a lot of it is we need to understand the true genetic mechanisms underpinning a lot of the conditions that we see, we don't have all that information. We need better evidence-based guidelines for care because like I said earlier we have guidelines but we need more evidence to support those of course. And I think that we also need a much better understanding of how people living with Turner Syndrome are doing psychosocially, emotionally, physically. There's a lot to be said and we've talked about this in a lot of our genetics episodes about involving people living with these conditions in the research, not merely as subjects of research. So yeah, that is Turner Syndrome.
Erin Welsh	There's a lot. I think I've already said this but there's just so much there.
Erin Allmann Updyke	One of the things that really excites me about this is just talking about the variety inherent in sex chromosomes and sex determination because it is so much more interesting than the black and white that we learned in school.
Erin Welsh	Right. I mean the black and white, we learn that way because it's convenient, right.

Erin Allmann Updyke	Yeah.
Erin Welsh	But it's not accurate.
Erin Allmann Updyke	Right.
Erin Welsh	And you're missing out if that's how you're looking at sex as this irreversible constant thing. There are so many different ways to do define it. It's really cool.
Erin Allmann Updyke	It's really cool. And yeah, I think it also makes us think that there is one thing that is normal and the rest of everything outside of that is abnormal which isn't the case.
Erin Welsh	Yeah.
Erin Allmann Updyke	There's a lot of variation in what can happen during the process of development, during the process of cell replication and division. It's awesome.
Erin Welsh	It is.
Erin Allmann Updyke	So.
Erin Welsh	So. Sources?
Erin Allmann Updyke	Sources? So everyone can read some more.
Erin Welsh	Let's do it. I have several. I'm gonna shout out a couple that I found super helpful. One is by Abbott et al from 2017 about the history of sex chromosome discovery. A paper by Brush 1978, that was the one about Nettie Stevens, it's a great paper. And then also I got some info from a book by Sarah Richardson called 'Sex Itself'. And then finally I just want to shout out again that great paper by Moore and Roberts from 2013 called 'Polygenic Sex Determination'.
Erin Allmann Updyke	I had a number of papers, a couple of my favorites that are more recent. One was 'Turner Syndrome Mechanisms and Management' from Nature Reviews Endocrinology 2019 and another was 'The changing face of Turner Syndrome' from Endocrine Reviews 2022. Both of those have a lot on where we stand with Turner Syndrome, what we know, and what we need to know. But we'll post the list of all of our sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com. Go check it out.
Erin Welsh	I want to give a special thank you to Emily Moore who helped me talk through this part of my history for this episode. You're the best, thank you.
Erin Allmann Updyke	And thank you again to Katie, the provider of our firsthand account. Thank you so much for sharing your story with us and all of our listeners.
Erin Welsh	I mean we can't thank you enough. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you as always to the Exactly Right network.
Erin Welsh	And thank you to you, listeners. We hope that you liked this and that we did okay.

Erin Allmann Updyke	Yeah. Let us know one way or the other.
Erin Welsh	Yeah.
Erin Allmann Updyke	But I had a lot of fun.
Erin Welsh	I did too.
Erin Allmann Updyke	And a special thank you to our patrons. Thank you so much for your support, it means the world to us.
Erin Welsh	It really does. Okay well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.