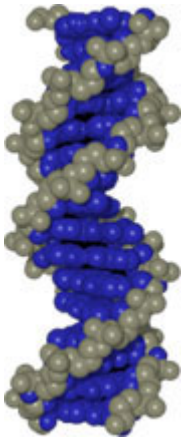

Gender:
In the Genes or in the Jeans?

A Case Study on Sexual Differentiation

Part I - "How are Males and Females Different?"

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Questions

1. What are the biological differences between males and females? Brainstorm with your group and come up with as many differences as you can.

Males	Females

2. When faced with a large number of things, scientists often find it useful to group them into a smaller number of categories. After you have completed your list, divide your characteristics into categories.

Category	Males	Females

Part II - "Chromosomal Sex"

Section A

Terry enjoyed biology lab. She was especially thrilled that today's class involved looking at her own cells under the microscope. Like the other ninth graders, she and her lab partner, Robert, had each taken a swab full of cells from inside their cheeks, smeared them on a few microscope slides, and stained them with cresyl violet. Now, as they examined them under the microscope, they searched for those dark bodies that Mr. Wilson had told them to look for.

"Okay, which one of us is supposed to have that Barr body?" Terry asked.

"Whatever body you have is fine with me," answered Robert.

Terry rolled her eyes and ignored him as she grabbed another slide to put under the microscope. "Hey, I still can't find any," she said. "What are they supposed to look like again?"

Finally, Terry and Robert called Mr. Wilson over to look at their slides. "Don't worry about it," he said. "The way the cells are put on the slide makes it difficult to see the inactivated X chromosome in all of a girl's cells. Look at Melissa's sample to see what the Barr body looks like."

Mr. Wilson called the class to attention. "So, what did you learn? Robert, how are male chromosomes different from female?"

"We're better," Robert said with a smirk, "cause we've got something the girls don't -- a Y chromosome."

"Oh, no," Terry retorted. "You guys are defective! You're missing something awesome that we've all got -- that second X chromosome!"

Mr. Wilson laughed as the bell rang. "Okay, it seems like you've all gotten the point. Females have two X chromosomes, while males have an X and a Y chromosome. Now, write up your lab reports, and I'll see you tomorrow."

Questions

1. Terry and Robert have mentioned two alternative hypotheses that might explain the role of sex chromosomes in determining the sex of an individual.

    - Hypothesis 1: Male development occurs because of the presence of a Y chromosome.
    - Hypothesis 2: Male development occurs because of the absence of a second X chromosome.

    Fill in the table below with the words "male" or "female" to indicate which phenotype you'd expect to see if Hypothesis 1 were correct, and which you'd expect if Hypothesis 2 were correct.

Gametes		**Zygote**	***Predicted* phenotype if "maleness" is determined by the ...**	
Egg	Sperm	Genotype of sex chromosomes	presence of a Y chromosome (Hypothesis 1)	absence of a second X chromosome (Hypothesis 2)
X	X	**XX**		
X	Y	**XY**		

2. Do the appearances of males and females allow us to distinguish between these two hypotheses?

Section B

The appearances of typical males and females do not allow us to differentiate between these hypotheses. But scientists have been able to differentiate between these two hypotheses by observing certain unusual situations.

Sometimes errors occur during the meiotic divisions that lead to gamete formation (sperm and eggs). Instead of each sex chromosome going to a different gamete, two of these chromosomes might fail to separate, and so end up going to a single gamete, while the sister gamete would then get no sex chromosome. In other words, gametes may occur that either lack any sex chromosome or that have extra sex chromosomes.

If one of these gametes participates in fertilization, a zygote is produced with a genotype that differs from the usual XX and XY. By observing these uncommon genotypes, scientists are able to differentiate between these two alternative hypotheses.

Fill in the table below with the words "male" or "female" to indicate which phenotype you'd expect to see if hypothesis 1 were correct, and which you'd expect if hypothesis 2 were correct.

Gametes		**Zygote**	***Predicted* phenotype if "maleness" is determined by the ...**	
Egg	Sperm	Genotype of sex chromosomes	(1) presence of a Y chromosome	(2) absence of a second X chromosome
X	O	**X**		
XX	X	**XXX**		
X	YY	**XYY**		
XX	Y	**XXY**		
XX	YY	**XXYY**		
O	Y	**Y**		

Questions

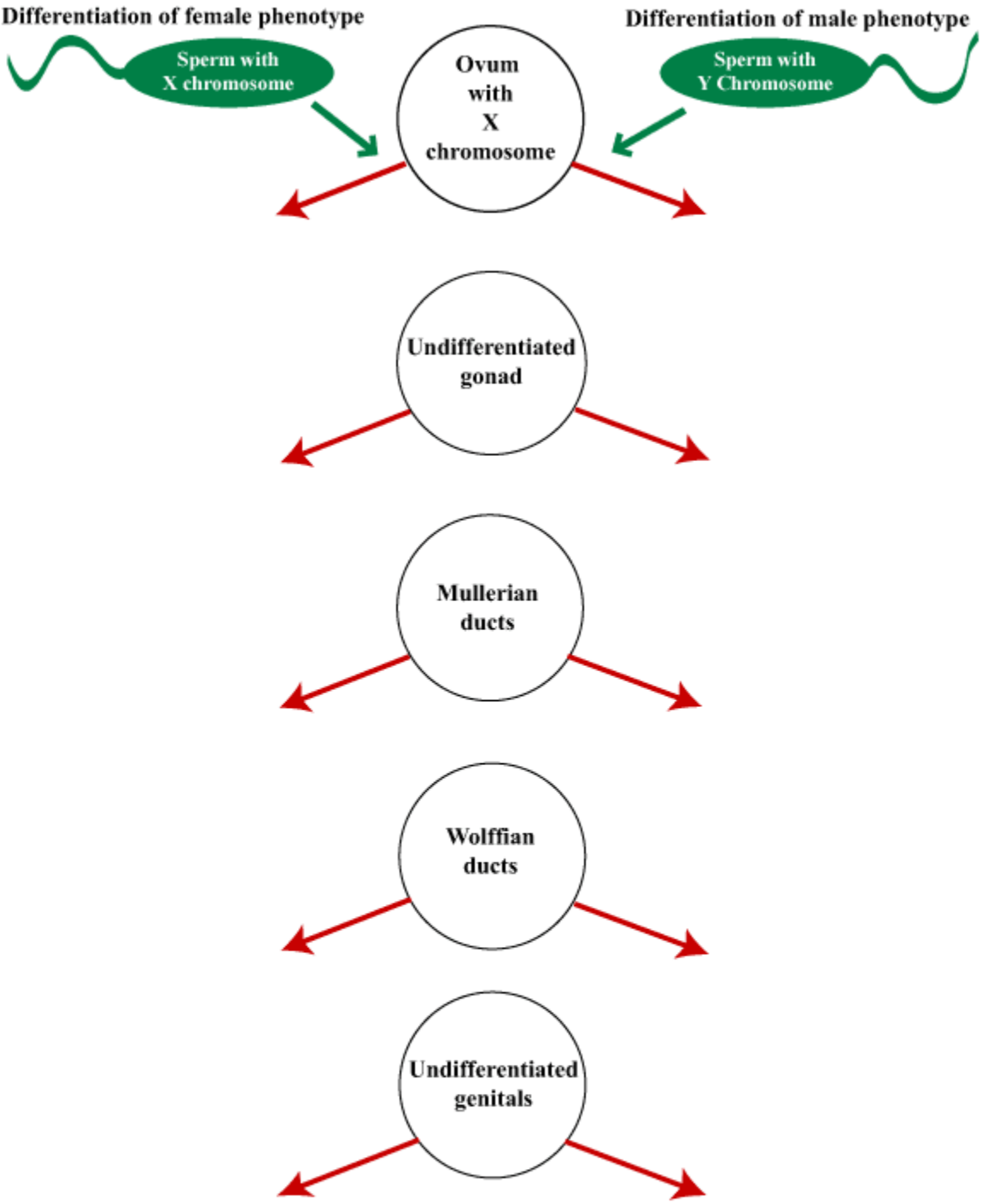
1. Which of these individual(s) would allow you to distinguish between these two hypotheses?
2. What phenotypes actually develop in the conditions described in this table?

3. Based on this evidence, which hypothesis now seems to better explain the role of sex chromosomes in determining an individual's sex?

4. Based on what you know so far, what is the logical explanation for Terry's inability to find a Barr body in her buccal smear?

5. Fill in the chromosome part of the flowchart to indicate what determines sexual differentiation at the level of the chromosomes.

Flowchart


Differentiation of female phenotype
Sperm with X chromosome
Ovum with X chromosome
Differentiation of male phenotype
Sperm with Y Chromosome
Undifferentiated gonad
Mullerian ducts
Wolffian ducts
Undifferentiated genitals

Part III - "Gonadal Differentiation"

Section A

Just how does the Y chromosome determine maleness? In 1990, scientists found that the crucial part of the chromosome was a segment on the short arm, which they called SRY, for Sex-determining Region of the Y chromosome. Subsequently this was narrowed down even further, with the discovery of a crucial gene. When this gene was injected into a fertilized mouse egg with an XX genotype, the eggs developed into a mouse with testes. (In fact, mice produced in this way were male in all respects, not just their gonads--they had male genitals and, as adults, they behaved like normal males would when an adult female was in the vicinity.) The protein that this gene coded for was called TDF, for Testes Determining Factor, and this single gene seemed to act like a switch, turning on the development of the male gonad.

Does the same gene cause the gonads to develop into testes in humans, too? Obviously, we can't conduct comparable experiments on humans. But once again, we can look for "experiments of nature," where these conditions naturally occur.

During meiosis, a process called translocation sometimes occurs in which a gene on one chromosome may move to another chromosome that happens to be nearby. After screening thousands of people, scientists have found that this process may occur with the SRY gene.

Questions

1. Assume that differentiation of gonads in humans works in a way similar to that in mice. What kind of gonad would you expect to develop in each of these conditions?

    a. An individual who has XX chromosomes, with a translocated SRY gene attached to one X chromosome.

    b. An individual who has XY chromosomes, but the SRY gene has been permanently deleted from the Y chromosome.

2. What do these results tell you about the factors that are normally responsible for the differentiation of male and female gonads? Fill in the gonad part of the flowchart to reflect your answer.

Section B

After school that day Terry went to the mall with her friends Tiffany and Melissa. They were excitedly getting ready for summer camp and shopping for swimsuits. They always had a great time at the mall, trying on makeup and perfume, picking out clothes, and checking out guys. Terry came out of the dressing room modeling a shocking pink bikini.

"Hey, what's that?" asked Tiffany, pointing to some small scars just above Terry's bikini line.

"It's nothing," Terry answered. "Some kind of operation I had as a baby. I don't even remember it."

Just then Melissa dashed over with a turquoise swimsuit. "Oh, Ter, this is so you!" she squealed, interrupting their conversation.

Terry loved it, and ended up buying *both* suits.

Later that night as Terry was lying in bed, she ran her fingers idyly across the scars on her abdomen. What was it her mother had told her about that operation? Something about "boy stuff" that got into her by mistake, before she was even born, and they had to take it out.... "Boy stuff?!?" What could that mean? What do boys have inside there? Terry pulled her biology book off the shelf and flipped to the picture of the reproductive system. Gonads.... Testes.... Did she have testes before she was born...? "But that can't be," she thought, "I'm a girl!"

Questions

1. Terry doesn't realize it yet, but she *did* have testes when she was born. Consider this fact together with the results of Terry's biology lab and suggest two scenarios that might explain these results.

2. Is either of these scenarios a satisfactory explanation of Terry's biological condition? Why or why not? (You may want to read again about the mouse experiment that was described earlier.)

Part IV - "Internal Genital Differentiation"

The Y chromosome directs differentiation of gonads in the male direction. Is this chromosome responsible for the other levels of sexual differentiation you came up with in Part I? Let's look next at the differentiation of male and female ducts.

The gonads are connected to the outside world by a system of ducts through which the gametes may travel. In the very young embryo, there are actually two sets of ducts present, called Mullerian and Wolffian after their discoverers. As the fetus develops, one set disintegrates while the other develops into the duct system appropriate for that sex.

In females, the Wolffian ducts disintegrate and the Mullerian ducts develop to become the oviduct, uterus, and the upper part of the vaginal canal. In males, Mullerian ducts disintegrate and the Wolffian ducts develop to become the vas deferens, epididymis, and seminal vesicles.

These changes occur when the gonad is developing, so scientists wondered if the Y chromosome itself doesn't determine duct differentiation, but rather something from the gonad causes the appropriate ducts to develop. The following set of experiments was conducted to find out.

Questions

1. Does the female gonad secrete something that causes the Mullerian ducts to develop and Wolffian ducts to disintegrate? The ovaries were removed from a group of female rats during early fetal development. After birth, these females and normal females were examined to see which ducts developed. (A + indicates that this duct did develop, a - indicates that it disintegrated.)

Experiment	Mullerian	Wolffian
Normal female	+	-
Remove ovaries	+	-

   What would you conclude about the role of the ovary in causing differentiation of the ducts in females?

2. Does the male gonad secrete something that affects male differentiation? In this experiment, the testes were removed from a developing fetus and the subsequent development of the ducts was noted as follows:

Experiment	Mullerian	Wolffian
Normal male	-	+
Remove testes	+	-

   What would you conclude now about the role of the testes in causing differentiation of the ducts in males?

3. The testes secrete testosterone. Is this hormone responsible for Wolffian duct development and Mullerian duct disintegration? In one experiment, scientists removed the testes and injected testosterone into the male fetuses. In another experiment, they used normal males with their testes intact and into these animals they injected a drug that has an anti-testosterone effect, that is, it prevents testosterone from acting. Here are the results:

Experiment	**Mullerian**	**Wolffian**
Normal male	-	+
Remove testes	+	-
Remove testes and inject testosterone	+	+
Intact male + anti-testosterone	-	-

What would you conclude now about the role of testosterone in differentiation of the male ducts?

4. Let's look at one more experiment on a male fetus. In this case the experimental manipulation was to remove the gonad from one side only. The results are presented below:

Experiment	**Mullerian**	**Wolffian**
Normal male	-	+
Remove testes	+	-
Remove left testis only and observe left side	+	+
Remove left testis only and observe right side	-	+

What would you conclude now about the role of the testes in differentiation of the male ducts?

5. Fill in your flowchart to indicate the differentiation of the Wolffian and Mullerian ducts.

Part V - "External Genital Differentiation"

Section A

We've seen different processes involved in differentiation of the gonads and the ducts. The gonads begin as a single tissue that can differentiate in either the male or female direction, depending on whether or not a Y chromosome is present. But when it comes to differentiation of the ducts, the Y chromosome is not important. Rather, the ducts begin as two sets of tissues, each of which can differentiate in only one direction (either male or female) depending on whether or not testicular endocrine and paracrine signals are present.

What about the external genitals? When we look at these in the early embryo, we see that their development seems to be like the gonads, that is, the male and female genitals are indistinguishable until about four to eight weeks of fetal life, at which time the tissue develops in either a male or female direction.

What regulates differentiation of the external genitals? The chromosomes or the hormones?

Questions

1. Design an experiment using laboratory rats to distinguish between these two possibilities. What results would you expect if the chromosomes are responsible? What results would you expect if the hormones are responsible?

2. Fill in the flowchart to reflect differentiation of the genitals.

Section B

Experimental work on laboratory animals showed that testosterone treatment of XX fetuses causes them to develop male genitals. Although we cannot ethically perform such experiments on human fetuses, there are some naturally occurring situations that support this hypothesis in humans too. In some extremely rare cases, pregnant women were found to have a testosterone-secreting tumor and their XX offspring were born with male genitals. The general consensus was that prenatal testosterone causes male genital differentiation.

This idea was modified in the 1970s, when some people were described with an unusual condition. At birth, their genitals were..., well, it was hard to tell. Their families lived in a small village, far from medical facilities, and since the babies sort of looked like girls, they were raised as girls. They went through puberty at around the usual age, but they didn't menstruate and develop breasts. Rather, it was their muscles that developed, voices deepened, and what had looked like a clitoris began to enlarge and appear more like a penis. In short, at puberty, these "girls" began to look more and more like adult males, and began to behave in ways typical of males in that village, including marrying a woman.

When they reached the attention of the medical community, the condition could be described medically as follows: XY chromosome, testes (which were undescended, so not noticeable), Wolffian duct development, no Mullerian duct, and blood levels of testosterone similar to that of a typical male. Very much like normal males! Just one small difference was noted. They lacked an enzyme called 5-alpha reductase, which converts testosterone to a related molecule, dihydrotestosterone, or DHT.

Questions

1. What would you now conclude about the differentiation of the male genitals?

2. Revise your flowchart to indicate the process of differentiation of the genitals.

Part VI - "Social Implications"

Section A

Terry looked like a normal 14-year-old with typically developed breasts. But she was worried. All of her friends had been having their periods for a couple of years while she hadn't started to menstruate at all. Her mother told her it was nothing to worry about. She reassured Terry that it was probably because she was a dancer and that often physically active girls started menstruating at a later age.

Terry's boyfriend David not only adored her beautiful hair and figure, but he was someone Terry could confide in about anything. She told him she was concerned about not having started to menstruate.

"Hey, you're lucky!" My sister is a fright when she gets her period."

"Yeah, I've seen her!" Terry laughed. "But seriously, I'm getting a little worried. All my girlfriends have already started."

"Did you talk to your Mom about it?"

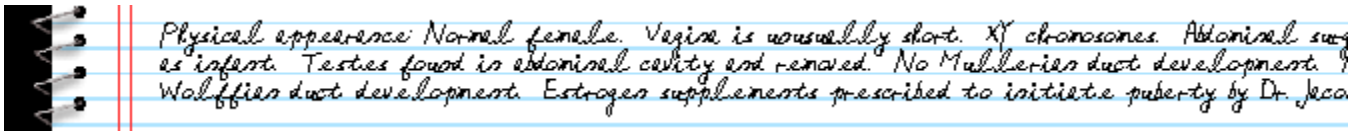
"She says not to worry. But I'm not sure that she really knows anything."

"Well, you could go to a doctor and find out. There's that Dr. Hunter who came to talk to us in sex-ed, remember? She seemed really nice, and she said we could visit her if we had questions. She works at Planned Parenthood over on the east side of town. It's right near the dance school you go to on Thursdays, so you could stop there after your class."

At her Thursday appointment, Dr. Hunter looked at Terry's body, took a blood sample, performed a pelvic exam, and asked Terry to come back the following week to discuss the results.

"Oh," she called after Terry as she was leaving. "Is it okay if I call your pediatrician? It's always helpful to speak with a doctor who is familiar with your medical history." "Sure," Terry answered. "It's Dr. Jacobs. He's known me since I was a baby."

The following week, the nurse brought Terry's folder to Dr. Hunter. Knowing that Terry was in the waiting room, she looked at the notes written there and wondered how to break the news to her patient.



Physical appearance: Normal female. Vagina is unusually short. XY chromosomes. Abdominal surgery as infant. Testes found in abdominal cavity and removed. No Mullerian duct development. No Wolffian duct development. Estrogen supplements prescribed to initiate puberty by Dr. Jacobs.

Question

1. Look at your flowchart and suggest a way to explain how Terry could have the outward appearance of a female, but still have the lab results described above.

Section B

Dr. Hunter told Terry that she was born with a condition called "Androgen Insensitivity Syndrome," and that when she was a baby, nonfunctional testes were found in her abdomen and removed to prevent the development of cancer.

"You haven't menstruated because you don't have ovaries or a uterus," she said. "And you won't be able to have children. You know those 'vitamins' your parents make you take that were prescribed by Dr. Jacobs? Those are really female hormones, to give your body a more feminine appearance. And it obviously works! You're a perfectly healthy young woman in every other way. "

Terry was thoughtful as she left the doctor's office and hopped on the bus to David's house.

"I just had to talk to someone," she said. "I had been wondering about this for so long, and now it seems like a relief, in a sense, to know what the truth is. The doctor explained that I won't be able to have children, but I could always adopt. But I'm so mad at my parents! How could they not tell me this? They knew I had that operation as a baby. I mean, it's my body! Were they trying to protect me or something? What did they think, that if I knew I couldn't get pregnant, I would be having sex all over the place? I'm not a baby anymore. Shouldn't I be the one to say what's for my own good?"

Terry had been rattling on, trying to get out her many mixed-up thoughts, but now she stopped for a breath and looked at David for support.

He was just staring at her. When he finally spoke, the words came out slowly, "You mean ... I've been dating ... a boy?"

Questions

1. Most people have a sex that is consistent on all levels: genetic, gonadal, internal genitals, external genitals. But sometimes there are discrepancies, as we've seen. In these cases, how should one determine whether a person is considered male or female? Is Terry a male or a female?

2. At what age should adults tell a child that he or she has such discrepancies?

3. Adults often make medical decisions about young children, such as the decision to remove gonads that have the potential to become cancerous. Who should be responsible for making such decisions, the physician or the parent? Or would you say that neither has that right? Should they wait until the child is old enough to decide?

4. Is it legal for Terry to marry? If Terry becomes engaged, should he/she tell her future husband/wife?

5. What is the likelihood that Terry's siblings are affected by this condition?

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