ADAM MARTIN: Well, first of all, nice job on the exam. We were quite pleased with how you guys did. And so from now on in the course, Professor Imperiali has been telling you about information flow, but information flow within itself, so information flow from the DNA to the proteins that are made in the cell, which determines what that cell does. And so we're going to switch directions today. And we're going to start talking about how information flows between cells-- so from a parent cell to its daughter cells. And we're also going to talk about how information flows from generation to the next.

And this, of course, is the study of genetics. And what genetics is as a discipline is it is the study of genes and their inheritance. And the genes that you inherit influences what is known as your phenotype. And what phenotype is is simply the set of traits that define you. So you can think of it as a set of observable traits.

And this involves your genes, as you probably know. I mean, just this morning, I was dropping my son off at school, and he was comparing how tall he was compared to his classmates. And as he went in, he was like, thanks for the genes, dad. So I expect that many of you are going to be familiar with much of what we'll discuss, but we're going to lay a real solid foundation, because it's really fundamental for understanding the rules of inheritance and how that works.

So genetics is the study of genes. So what is a gene? You can think about genes in different ways. And what we've been talking about up until now, we've been talking about molecular biology and what is known as the central dogma. And the central dogma states that the source of the code is in the DNA. And there's an information flow from a piece of DNA, which is a gene. And the gene is a piece of DNA that then encodes some sort of RNA, such as a messenger RNA. And many of these RNAs can make specific proteins that do things in your cells in your body. So that's one very molecular picture of a gene.

You can think of a gene as a string of nucleotides. And there might be a reading frame in those nucleotides that encodes a protein. So that's a very molecular picture of a gene. The field of genetics started well before we knew about DNA, and its importance, and what the DNA encoded RNA which encoded proteins. So the concept of a gene is much older than that.

And so another way you can think of a gene is it's essentially the functional unit of heredity. So it's the functional unit of heredity. I'll bump this up. So I want to just briefly pause and kind of

give you an overview of why I think genetics is so important.

So what you saw up here is you saw a cell divide. And I showed you this in the last lecture-- you saw the chromosomes, which are here, how they're segregated to different daughters. And this is-- basically, you're seeing the information flow from the parent cell into the daughter herself. But we saw this, so I'm just going to skip ahead.

So why is this so important? I'm going to give you a fairly grandiose view of why genetics is so important. And I'm going to say that we can make a good argument that genetics is responsible for the rise of modern civilization. Humans, as a species, began manipulating genes and genetics even before we had any understanding of what was going on. So this is more of an unconscious selection.

And so 10,000 years ago, humans were hunter gatherers. They'd go out, and try to find nuts and seeds, and hunt animals. And that's how we got our food. But around 10,000 years ago was the first example of where humans, as a species, really altered the phenotype of a plant, in this case. So wild wheat and wild barley, the seeds develop in a pod. And the biology of the wild wheat is such that the pod shatters, and the seeds then spread on the ground where they can then germinate into new plants.

But 10,000 years ago, humans decided that it would be more ideal if we had a form of wheat which didn't shatter, which is known as non-shattering wheat in which the seeds remain on the plant. And that allows it to be easily harvested at the end of the season. So 10,000 years ago is one of the first examples where humans really genetically altered the phenotype of a plant. And they selected for this non-shattering wheat, which then allowed for the rise of agriculture.

In addition to wheat, we also-- about 4,000 years ago was the rise of domesticated fruit and nuts. So here are some almonds. If you would like an almond, feel free to have some. You guys want some almonds? No. If you have a nut allergy, don't eat them. Great.

So wild almonds, when you chew them, there's an enzymatic reaction that results in cyanide forming. Rachel just stopped chewing. Don't worry. These are almonds that are harvested at Trader Joe's, so you're safe. And so the wild almonds, obviously, were not compatible for consumption. But 4,000 years ago, humans again selected for a form of the almond, which involved just a single gene, which was non-bitter and known as a sweet almond, which was also not toxic.

So this doesn't just go for foods, but also for clothing. So humans have selected for cotton with long lint. And that served as a basis for clothing and sort of allowing us to have fabric. And I just want to end with a little story about the almond, which is part of the archaeological evidence for when almonds were domesticated was when King Tut's tomb was unearthed. And they found a pile of almonds next to the tomb, because the Egyptian culture, what they did is they buried the dead with food to sustain them in the afterlife. So that just gives you an idea as to how far back the importance of genetics goes.

If we think about nowadays, right now you are always seeing genetics in the news. And you also have the opportunity yourself to sort of do your own genetic experiment. And so now you guys are undoubtedly aware of all these companies that want you to send them your DNA. And they also want you to send them money, such that they can give you information about your family tree and also information about your health.

So this is now a big business. But if you don't understand genetics, this is not as useful as it could be. So I'm just curious. How many people here have used one of these services and had their DNA genotyped? Cool. And do you think that really changed your view of who you are? Or was it kind of, eh?

AUDIENCE: We actually-- I don't know if we even looked at where we came from. We looked for genetic disease.

ADAM MARTIN: So you're looking for genetic disorders. And you don't have to tell me anything about that. Yeah, so I have not done this, but my dad has done it. And he will go find his relatives and bore them with our ancestry. So this is one example of how genetics is really in play today. And not everyone knows how this works. I've had people at Starbucks in the morning come up to me with their 23andMe profile and ask me to explain stuff, because they know who I am. It's a little awkward.

So we can also use genetics for forensics. And so this is kind of a-- I had a lab manager in the lab, and he told me that people were doing this in senior homes in Florida, which I thought was kind of funny. What I find hilarious about this is the mug shot of the dog. That dog looks so guilty. But you can use DNA to-- you can use DNA to genotype poop. You can genotype your neighbor's dog. You can get evidence that they're the one that's pooping on your lawn. So that's a not-so-serious example.

But there are more serious examples of where DNA genotyping is really having an effect in our

society. And this is something I mentioned in the intro lecture. Just this past spring, someone was suspected as being the Golden State Killer. This is a cold case. The killings happened 40 years ago, but the break came from investigators getting DNA from the suspect's relatives to implicate this person in this crime. So they had DNA from the crime. And they saw that there were matches to the DNA at the crime to certain people. And then they can reconstruct who might be the person in the right place to commit the crime.

So this is-- I think this is interesting, because it also leads to all sorts of privacy issues, right? Who's going to gain access to your genotype if you submitted to these companies, right? I mean, this is probably a case where I'd argue there's probably a beneficial result in that you can actually figure out if someone's committed a crime. But there are other issues in terms of thinking about insurance companies where we might be interested in having our information not publicly available to insurance companies. And maybe this is something we can discuss later on in another lecture.

For today, I want to move on and go through really the fundamentals of genetics. And what I'm going to do is I'm going to start with the answer. OK? I'm going to present to you guys today the physical model for how inheritance happens. OK? So today, we're going to go over the physical model of inheritance.

And this physical model involves cell division, which you saw in the last lecture and also in my opening slide. It involves cell division and the physical segregation of the chromosomes during cell division. So also chromosome segregation.

OK, so this is how I'm going to represent chromosomes. And I just want to step you through what it all means. So I have these two arms that are attached to this central circle. The circle is meant to represent the centromere. So this is the centromere.

And you'll remember from the last lecture on Monday, the centromere is the piece of the chromosome that physically is attached to the microtubules that are going to pull the chromosomes to separate poles. OK? So that's called the centromere. And usually, it's denoted, it's like a constriction in the chromosome or a little circle. OK?

These other parts of the chromosome are the chromosome. So that you have the arms of the chromosome. Now I'm drawing what's known as a metacentric chromosome. It's not important that you know that term. But it just means that the centromere is in the middle of the chromosome. There are other types of chromosomes with the centromere might be at the

end. OK? So there are different types of chromosomes.

All right, now, for all of us, we have cells that have different numbers of chromosomes. OK? Some of our cells are what is known as haploid. And what I mean by haploid is there is a single set of chromosomes. Now the cells that we have that are haploid are our gametes, so they're our eggs and our sperm cells. OK? So these include gametes.

OK, but most of the cells in your body are what is known as diploid. And diploid means there's two complete sets of chromosomes. OK, and you get one set from one parent, the other set from the other parent. OK? So one set from each parent.

OK, and I'll draw the other set like this. And what I'll do is I'll just shade in this one to denote that it's different. OK? So these two chromosomes then are what is known as homologous. They're homologous chromosomes. Homologous.

OK, and what I mean by them being homologous is that, basically, these two chromosomes have the same set of genes. OK, so they have the same genes. They have the same genes. But they have different variants of those genes. OK, so different variants of these genes. And these variants are referred to as alleles. OK? So if you have the same gene but they differ slightly in their nucleic acid sequence, then they're distinct alleles of those genes.

So often, the way geneticists refer to these different variants or alleles is we use a capital letter and a lower case letter. OK, so this chromosome over here might have a gene that's allele capital a. And then this homologous chromosome will have the same gene but a different allele, which I'll denote lowercase a. OK?

So in this case, big A and little a are different alleles of the same gene. They might produce a slightly different protein, which would result possibly in a different phenotype. OK? So everyone understand that distinction?

Oh, I want to make one point because this came up last semester and was one of those cases where I forgot the part about the head. So we often just have two alleles when we teach genetics. But I hope you can see that because a gene is a long sequence of DNA, there is a ton of different alleles you can have within a given gene. So one nucleotide difference in that gene would result in a different allele. OK? So we often refer to two alleles, but there can be more than two alleles for a given gene. OK? Does everyone see how that manifests itself? OK, great. Any questions up until now? Yes, Carmen?

AUDIENCE: So when you say that there's more than one, more than just the two alleles, I don't have more than one on each chromosome. So they're just more than one--

ADAM MARTIN: In the population. So Carmen asked, well, can I have like five alleles of a gene? And that's a great question. And so thank you, Carmen, for asking that. What I mean is if we consider a population as a whole, right?

You have two alleles of each gene, unless it's a gene that somehow duplicated. And so when we're considering the population, there can be more than-- right? I mean, I see we have people with-- hair color is not a monogenic trait. But we have people with black hair, with blond hair, with brown hair, right? There is more than just two possible alleles with possible phenotypes. OK?

All right, let's go up with this. All right, now I want to start at the beginning. So most of our cells are diploid. And the origin of our first diploid cell is from the union of two gametes. OK? So I'm going to draw two gametes here. Each is one n.

And I'm just going to draw one set of chromosomes for this here. So we might have a male gamete and a female gamete. And what I'm referring to when I say n here, n is basically referring to the number of chromosomes per haploid genome. So when you have one n, it means you're haploid because you have only one set of haploid genome.

But early in your life, we're all the result of a fusion between a male and female gamete. And so that creates a diploid cell. OK, so now, this diploid zygote, so this is referred to as the zygote, is diploid and now has a set of homologous chromosomes. OK? So I'm only drawing one set of homologous chromosomes here.

So on the board, I'm going to stick to just one, so I don't have to draw them all out. In the slides, I have three. OK? So each of these represents a chromosome. These are different chromosomes. Different chromosomes are either different color or have a different centromere position. And then these down here that are colored are going to be the homologous chromosomes. OK? Do you see how I'm representing this?

OK, so once you have the zygote, right, so you guys are no longer one cell, right? You guys each are tens of trillions of cells. So this zygote cell had to reproduce itself, and your cells had to divide, so that you grew into an entire multicellular organism. I'll just quickly erase that.

OK, so when most of your cells divide, and most of your cells are known as somatic cells. When cells of your body or your intestine and your skin, when they divide, they genetically replicate themselves. And they're undergoing a type of cell division known as mitosis. OK?

In mitosis, it's essentially a cloning of a cell. Or ideally, it's the cloning of a cell. So you have a diploid cell. It has to undergo DNA replication . And when a chromosome undergoes DNA replication, it will, during mitosis look like this. OK?

And these two different arms or strands, they're known as sister chromatids. OK? So that's just another term you should know. These are sister chromatids. OK, and the sister chromatids, if DNA replication happens without any errors, should be exactly the same as each other in terms of nucleotide sequence. OK?

So after DNA replication, this cell will essentially have four times the amount of DNA as a haploid cell. And it will split into two cells. And again, they'll both be diploid. OK? And I'll just point out, if we're thinking about our pair of chromosomes here, right, this parent cell has both homologs. And the daughter cells, because they should be genetically identical, also have both homologs.

OK, so that's an example with just one chromosome. I'll take you through an example with these three chromosomes here-- all six chromosomes. So you have-- these are homologs. These are homologs. These are homologs. And during mitosis, all of these chromosomes initially are all over the nucleus.

But during mitosis, they will align along the equator of the cell and what is known as the metaphase plate. Metaphase is just a fancy term for one particular stage in the mitotic cycle. And then what will happen is the spindle will attach to either one side or the other side of these chromosomes.

And it will physically segregate them into different cells, OK? And what I hope you see here is that this has six chromosomes. This has six chromosomes. And these two daughter cells are genetically identical to the parent cell. OK, so this is known as an equational division, because it's totally equal. OK?

And again, the daughter cells are both diploid, OK? So that's mitosis. Any questions about mitosis? OK. Moving on, we're going to talk now about another type of cell. And these are your germ cells. And these germ cells undergo an alternative form of cell division known as meiosis,

OK? And your germ cells-- germ cells produce your egg and sperm.

And so meiosis essentially is producing gametes, such as egg and sperm cells, OK? So what's the final product going to be? What should be the genomic content of the final product of meiosis? It should be one end, right? Who said that? Sorry. Yeah, exactly right. What's your name?

AUDIENCE: Jeremy.

ADAM MARTIN: Jeremy. So Jeremy is exactly right. Right? The germ cells-- in order to reproduce sexually, they should be haploid cells, so that they can combine with another haploid to give rise to a diploid, OK? So the ultimate result that we want is to have cells that are one end.

But most of our cells to start out with are diploid, so they're two end, OK? So what's special about meiosis is you're not just going from two end to two end, but you're reducing the genetic content of the cells. You're going from two end to a one end content, OK?

So again, meiosis starts with DNA replication. But in this case, the first division, which is meiosis I, is not equal. And it actually segregates the homologs, such that you get one cell that has one of the homologs duplicated and another cell that has the other homolog duplicated. OK?

And I'll show this. I'll show it right now. So this is the same cell now. It's undergone DNA replication. As you can see, each chromosome has two copies. But instead of all the chromosomes lining up in the same position of the metaphase plate, what you see is that homologous chromosomes pair at the metaphase plate.

And what happens here is that the homologous chromosomes are separated-- two different cells. And now, you have two cells that are not genetically identical, OK? So because there is not equational and there's a reduction in the genetic material that's present in the cells, this is known as a reductional division, OK?

So that's meiosis I. And that's a reductional division. And then-- but this is not yet haploid. And so-- here, I'll just stick another one in here. These cells then undergo another round of division, which is known as meiosis II. And during this meiosis, these sister chromatids are separated, such that you're left with one chromosome.

And my drawing-- at least one chromosome per gamete, OK? So each of these, then, is 1n.

OK? So again, you have the chromosomes. But this time, you have them aligned like in mitosis. They align. The sister chromatids are physically separated.

And now, you see this cell is genetically identical to this cell. And this cell here is genetically identical to this cell, OK? So that's meiosis II. And that's an equational division much more like mitosis, OK? Because the product of the division of those two cells-- each of those is equal, OK?

And finally, the result of meiosis II is that you're then left with gametes that have a haploid content of their genome. OK, I want to end lecture by doing a demonstration. Let's see. So this could either be amazing, or it will be a complete disaster. So we're totally going to do it. So everyone come up. Right here. Here.

Evelyn, you can leave when you have to go. And we'll have a chromosome loss event. OK? It has to be a multiple of four. If we have extra people label, then the people can supervise. Go. Oops, sorry. All right. What do we got here? Here you go, Bret, Andrew. Sorry. I hope I'm not hitting anybody.

AUDIENCE: [INAUDIBLE]

ADAM MARTIN: What's that? Yeah, that's the advantage of these. All right. Here you go, Myles. Let's see. Here you go. Sorry. Someone take this. All right. What do we got here? Just got a little chromosome here.

AUDIENCE: [INAUDIBLE]

ADAM MARTIN: Oops, sorry. All right. Who doesn't have a chromosome? Everyone in the class has a chromosome? All right. One of you want to come in here? All right. We'll see how constrained we are in terms of space.

I've never been this ambitious and had this many chromosomes before, so I'm excited to see how this works. So you each have a Swim Noodle. They're different colors, so different colors represent different chromosomes. And then you also have Swim Noodles that have tape on them.

And these represent different alleles from your other chromosomes. So these two chromosomes would be homologs of each other, OK? Does that make sense? OK, great. All right. Now, the metaphase plate will be along the center of the room.

So let's first reenact mitosis. So why don't you guys find your sister chromatid and then sort of align in the middle of the room here? Sister or brother chromatid. How are we doing? Do we have enough space there? It's a little packed. You can see how the cell-- can you imagine how packed it is inside a cell?

OK, everyone found their sister chromatid. Normally, the sister chromatids-- they replicate and they get held together. So there's no finding of sister chromatids, but-- all right. Great. So segregate and we'll see how you guys did. All right. And the goal is that you guys would be genetically identical. So how-- OK, great.

That looks like one short red, one short red. OK, that's good. They look genetically identical to me. All right. So that was my mitosis. Now, we're going to do meiosis. OK, why don't you guys align, like what would happen during meiosis I. OK, you guys can come back. Think about who you're going to pair with.

[SIDE CONVERSATION]

All right. So what were you looking for when you were pairing? Who were you looking for?

AUDIENCE: Longest chromosome.

ADAM MARTIN: Your longest chromosome, right? OK, great. All right. Why don't you guys segregate? All right, so that was meiosis I. Meiosis I looks successful to me. And now, we have to undergo meiosis II. So maybe what we could do is you guys can rotate. And the metaphase spindle can be sort of in this orientation.

AUDIENCE: [INAUDIBLE]

ADAM MARTIN: Yeah, that will-- we want a group over there, a group over there, a group here, a group here. And those will be our four gametes.

[SIDE CONVERSATION]

All right. You guys set? All right. Go.

[SIDE CONVERSATION]

OK, terrific. Everyone haploid? Looks like everyone is haploid, which is good. Right? So let's just take a minute and think about probability here. So what was the probability that a gamete would end up with this orange allele on the red chromosome?

AUDIENCE: Half.

ADAM MARTIN: Half, right? Because there are two, right? So these two gametes have that allele. These two should not, right? OK, great. And we just had a chromosome loss, so that gamete is in trouble. But maybe we could get a TA to rescue this chromosome. Either one of you is fine. There you go, David.

[SIDE CONVERSATION]

All right. That was great. Now, let's-- as you're doing this, you get a sense as to how things could get mixed up, right? And you think inside the cell, right? So I don't-- I've lost track of how many chromosomes. We have 1, 2, 3, 4, 5, 6, right? How many chromosomes do we have?

AUDIENCE: 23.

ADAM MARTIN: We are-- a haploid set for us is how many chromosomes?

AUDIENCE: 23.

ADAM MARTIN: 23. Exactly. Right? So it'd be even worse for a human cell to get this to go right. So why don't you guys line up in the mitosis configuration? And we'll consider some things that could go wrong. All right. Who here is good friends with their sister or brother chromatid? Is anyone very good friends with their sister or brother chromatid?

[LAUGHTER]

AUDIENCE: [INAUDIBLE]

ADAM MARTIN: Yeah. Someone become good friends and become inseparable, OK? Would someone volunteer to be inseparable? OK, great. You guys are now inseparable, OK? Now, segregate. OK, great. Now, what happened there?

AUDIENCE: [INAUDIBLE]

ADAM MARTIN: What's that?

AUDIENCE: He stole her.

ADAM MARTIN: Yeah, that's cell stole her. OK. So now, we have two-- a duplication of that chromosome. What's happened over here with this daughter cell?

AUDIENCE: It's missing a chromosome.

ADAM MARTIN: It's missing a chromosome, right?

AUDIENCE: Right.

ADAM MARTIN: So these are the types of mistakes that can be associated with a cell becoming cancerous, right? Because let's say there was a gene that suppresses growth on that chromosome. And it wasn't on that homolog. Then you might result in a genetic sort of mutant or loss of that gene that would result in uncontrolled proliferation.

Also, picking up the extra copies of genes that promote growth could allow that cell to have a proliferative advantage, OK? We're going to-- this is sort of foreshadowing what we're going to talk about later. But I just want to plant the seed now. OK. Why don't we go back and do meiosis?

[SIDE CONVERSATION]

OK. Now, anyone see any friends looking across the aisle now? All right. Great. You guys are now inseparable. Why don't you guys segregate, except the inseparable ones? Oh, but your sister chromatids still have to stay attached. There you go. See? Great. Right. So just like last time, this is known as a non-disjunction event where the chromosomes don't separate when they should, OK? Great. Now, why don't you guys do meiosis II?

[SIDE CONVERSATION]

All right. You can segregate. All right. Now, you see these two gametes over here are lacking an entire orange chromosome. And these two gametes here have picked up an additional copy of an orange chromosome, OK?

So these two gametes are no longer haploid for the orange chromosome. And if one of these gametes were to fuse with a haploid gamete that has an orange chromosome, then now you

have a zygote that has three copies of the orange chromosome, which is abnormal, OK?

So if that were chromosome 21 in humans, that would result in something that's called trisomy 21, which is down syndrome, OK? So you see how mistakes in how chromosomes segregate can result in human disease. OK. Why don't we give yourselves a hand? Good job.

[APPLAUSE]

OK, you can just throw the Pool Noodles on the side. And I just have one slide to show you where we're going next. [INAUDIBLE]

[SIDE CONVERSATION]

AUDIENCE: So I have a question.

ADAM MARTIN: Yeah?

AUDIENCE: When the homologous chromosomes split, can you share alleles? Are there alleles preserved in this portion?

ADAM MARTIN: You're asking if there's crossing over?

AUDIENCE: Yeah.

ADAM MARTIN: There is crossing over. Yes. And that will get its own entire lecture. Yes, good question. OK, so just to give you guys a preview of what's up next. So in the next lecture, we're going to talk about Mendel and Mendel's peas. And we'll talk about the laws of inheritance, OK?

And realize Mendel was way before DNA or what our knowledge of a gene was, OK? Next, we'll talk about fruit flies, and Thomas Hunt Morgan, and seminal work that led to the chromosome model of inheritance and also resulted in the concepts of linkage and also genetic maps.

OK, we're going to go-- well, just to sort of anchor yourself, the structure of DNA was published in 1953. So these seminal genetic studies up here were done before we knew about DNA. So geneticists were studying genes and their behavior well before we knew DNA was what was responsible.

And then we'll talk about sequencing and the sequencing revolution. We'll talk about cloning,

and molecular biology, and how one might go from a human disease to a specific gene that causes it. And then, finally, we'll start talking about entire human genome and genome sequences. OK, so that's just a preview of where we're going, so have a great weekend.