Human Molecular Genetics
Prof. S. Ganesh
Department of Biological Sciences and Bioengineering
Indian Institute of Technology, Kanpur

Module - 01
Lecture - 04
Chromosome Structure and Function
(Organization; structure-function relationship; chromosome abnormalities)

Welcome to the fourth lecture of the first week of the course human molecular genetics. In the last three lectures we looked into how mutations affect the way the proteins are being made or how they function and so on.

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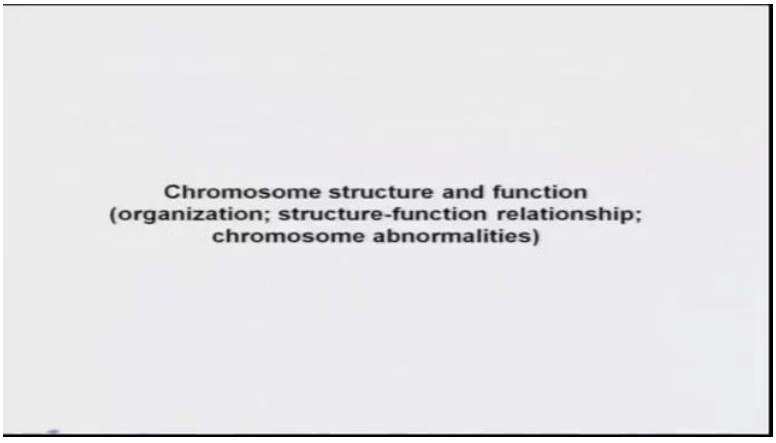

So, today we are going to look into a very different group of mutation. The mutation need not be affecting just one gene, but it could be a gross change, the way the chromosome is organized. A part of the chromosome is lost or it gains an extra copy or there is no net gain or loss, but the position of different region of the chromosomes are altered such a way that they no longer are able to function the way it should be. So this is called as chromosome structure and function. That's the broad topic of this particular lecture, wherein we will be looking into how the chromosomes are organized. We will give a brief overview as to how the chromosomes are organized and that would help us to discuss other elements in reference to human molecular genetics. Specifically we will be looking into chromosomal abnormalities. So what are chromosomes?

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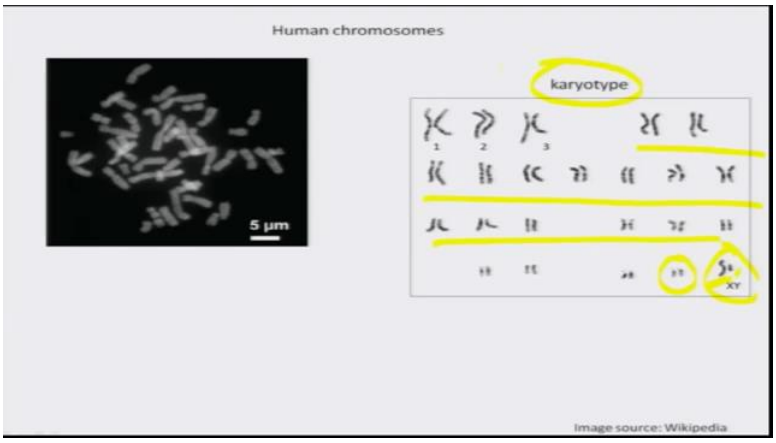

This is one of the classic images that would tell you that what you are looking at are chromosomes. So these are distinct, very compact structures that are present in our cell. So, normally when the cell is about to divide, what you call metaphase, the chromosome is at a, such a condensed stage, each chromosome attains a particular shape. That is what is shown here. So, if you are able to arrest the cell and you are able to view the chromosome, this is how they would look like and for a human what we do is, we take a picture of the chromosome and each chromosome, depending on their size, we order them. The one that is largest we call it as chromosome-1, the one that is smallest, you call as chromosome-22 and the remaining pair which has got X and Y chromosome are called as sex chromosome, because X and Y, their combination determine the sex. So, that is the 23rd pair.

So, if the individual for whom you are looking at the chromosome is a female, you would have two such long chromosomes that is XX. If the individual for whom you have made chromosome preparation is a male, then you would find an X chromosome and a Y chromosome, like what is shown here. So, this arrangement of chromosome based on their size and shape is called as karyotype and this is something that I would like you to remember. When you talk about karyotype, it is very important that you recollect this particular concept that the chromosomes are sorted based on their size and shape and I am able to identify each pair of the chromosome in a distinct way; that is very, very important.

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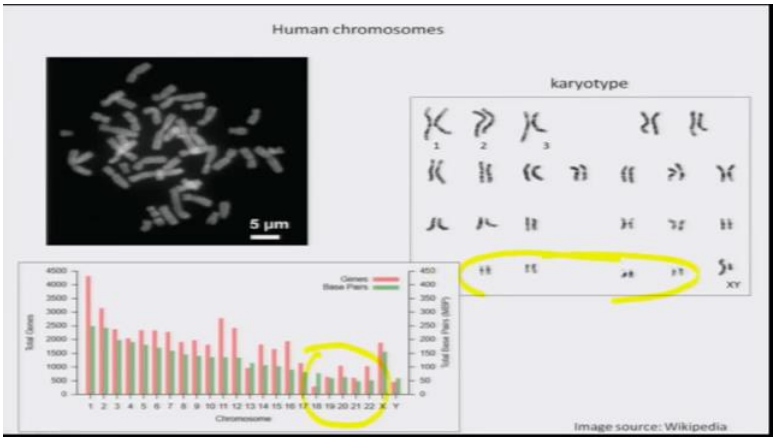

Now if we look into the chromosomes, as you could see in the karyotype, the chromosomes vary in their size; chromosome 1 being the largest and the chromosome 22 being the smallest, the chromosomes that are present in both in male and female. As a result, you can also expect the DNA that is present in each chromosome, vary according to its size; larger one will have longer DNA and smaller one would have smaller DNA. As a result, the number of genes that are present in each chromosome vary and that is shown in this particular bar diagram. So, you can see that chromosome 1 has got a large number of genes and chromosome 22 or the chromosome that belong to this group, over here, have fewer number of chromosomes, which is expected.

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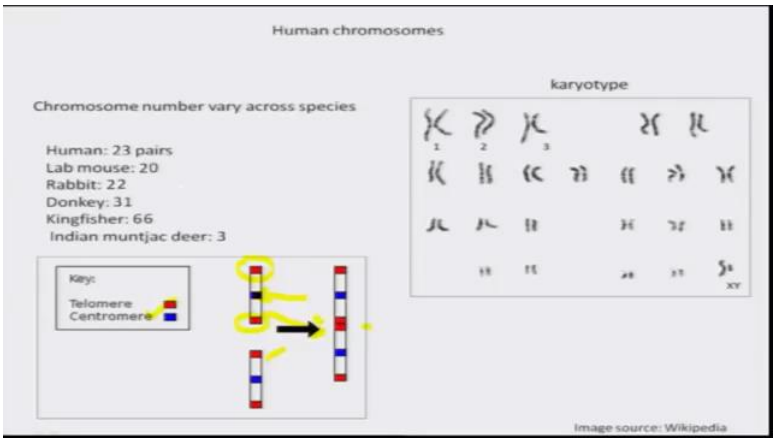

What is also interesting is the number of chromosomes. For humans, we know we have 23 pairs, which includes 22 chromosomes which you call as autosomes, meaning present in both male and female and the pair of sex chromosome that is X and Y. But, if we look into the number of chromosome, it varies from species to species. So, you have variation in terms of

the number of chromosomes that we have and among the mammals, we do have variations except for example if you remove the birds, in mammals; there is a variation in terms of numbers. But, what is known is the amount of DNA present in a cell is pretty much same, regardless of how many chromosomes you have. Therefore, variation in the number is either because of fusion, meaning two different chromosome fusing together to form a larger chromosome or they are broken to form shorter chromosomes and therefore the number varies. That is what we believe could be the reason why you have different number.

In the chromosomes, we have these elements. You have, on either end of the chromosome we have what is called as telomere, which help in protecting the chromosome from being lost, meaning being degraded and you have this region which is called as centromere, is a region on to which the kinetochore or the spindle fibers bind to and help in the segregation of the chromosome during a cell division.

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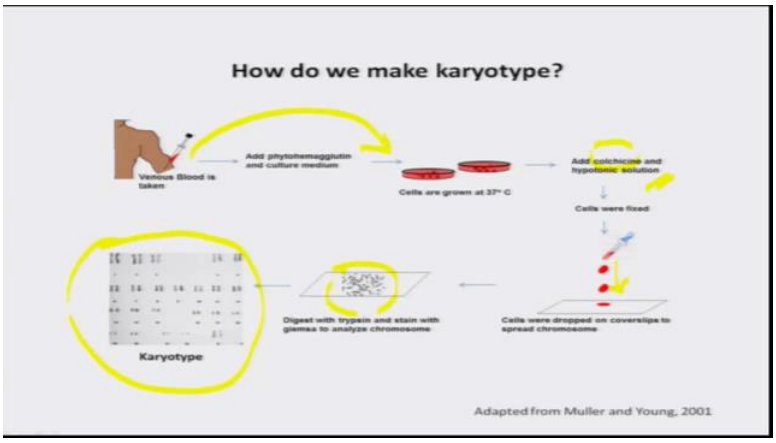

So, with this little introduction, let us look into how do you make karyotype? It is very interesting, because that the humans have 23 pairs of chromosomes was not known until early 1950's. Until then, it was not sure as to what is the number of chromosomes human have because of the challenge, the challenge being how do you look at chromosomes? It was extremely difficult then,

? So, they have developed a technique; in 1950's they have a technique to grow cells. Until then people have looked at chromosomes in tissues of dead individuals. They used to make sections to look at chromosomes. They were unable to find the number, because it was very

difficult to view all the chromosomes in any given section. So in 50's they developed a technique, wherein they are able to culture the human cell.

For example, you can take your blood and you have white blood cells in your blood, which can be cultured. You take the blood and then add, in dishes, where you can grow the cells, the white blood cells. They divide and then what do you do? When they are dividing you add to the medium a chemical called colchicine which does not allow the spindle to form. As a result, majority of the cells that are dividing they get arrested at the metaphase, where the chromosome is very compact waiting for the cell to pull the chromosomes to two poles therefore they can be, you know, put into the two daughter cells.

So, when majority of the cells are arrested at metaphase what you do is, you take the cells and then treat them with a solution called hypotonic solution. You give a mild salt concentration, therefore the cells swell, because they to, this osmosis process the cells swell and then you can drop them on a glass slide; because of the mechanical force, they burst open and then your chromosomes just spread out in the slide, which you can capture, the image can be captured using a microscope and you can make the karyotype as shown below. You can take an image and then cut the chromosome and sort them based on the size. So, this has really helped us in 50's to even understand that the male and female, two different sex of homo sapiens, humans, are determined by X and Y chromosome. That is why they are called as sex chromosomes.

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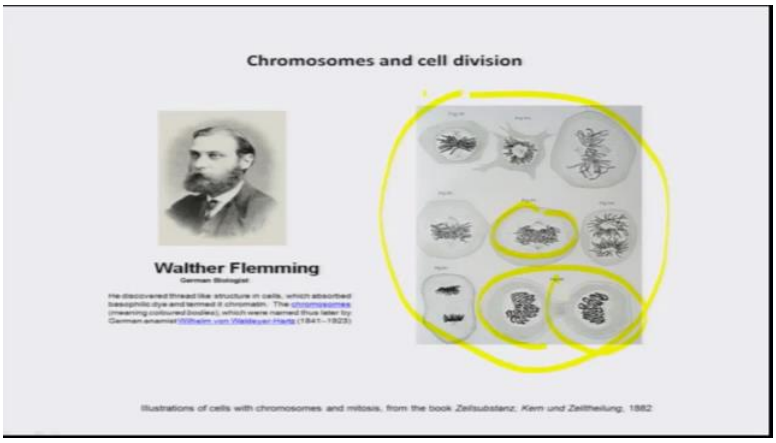

But the chromosome and their dynamic swing during the cell division, was understood much before by various scientists, one of them being Flemming. He is a German biologist, who

studied mostly plants because that is where the cell division to begin with were studied using plants, because of the soft tissue, people are able to press the tissue and stain it and they are able to see in the chromosome and these are one of those classic pictures, wherein this person is able to stain the chromosomes, look at the microscope and hand drawn pictures which gives all the details about this stage and what is the state? This is the metaphase and the cell is about to divide here and so on. We are able to tell that they represent different stages of the cell division; but he is able to show them so beautifully, we have understood.

So, what has been understood till then is that there are stages during the cell division and at certain stages of cell division, the chromosome really becomes very compact and you can use stains to distinguish these chromosomes; that is what you call now. But, when the cell is not at active division, when the cell is functional, then you will not be able to see individual chromosomes. This is called as interface, where it is, it is spread out everywhere in the nucleus.

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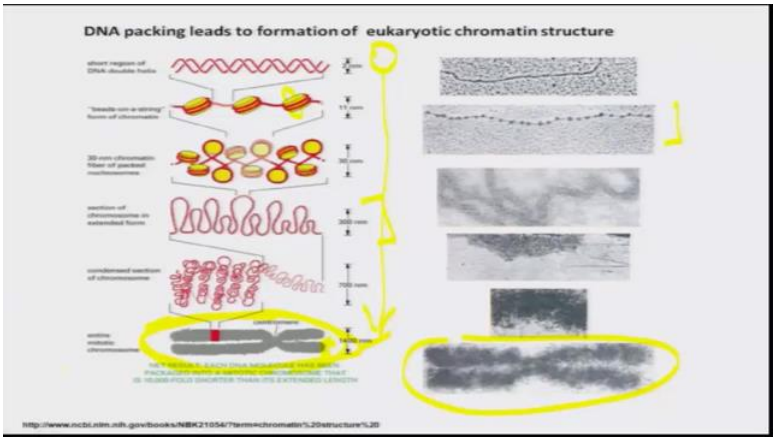

So, most of the chromosome studies, therefore are conducted using cells that are arrested in the metaphase. That is when you are having very compact chromosome, which is something, which is shown here. So, this is the schematic, this is the original picture of a metaphase chromosome. The chromosome that is very, very compact and you are able to stain them. So, what it is? This is a very highly compact stage of the chromosome and this is what you call as DNA. The DNA gets to this form during metaphase. How does it happen?

All of you know that you have a set of protein which you call as histones, on to which the DNA goes over to make it very compact and that is called as 11 or 10 nanometer structure, because that is how in the EM they look at and then, they form what is called solenoid structure and then of course you have a scaffold on to which the solenoid structure go over to give the kind of shape that you see as a metaphase. So, this is the different order by which the DNA or the chromatin, the DNA plus protein together they form very compact structure to arrive at something like this during the metaphase. So this happens, therefore the two copies of the chromosomes can easily be sorted out into the two daughter cells. Otherwise, you can imagine as to what would be the challenge for the cell to sort these individual DNA elements.

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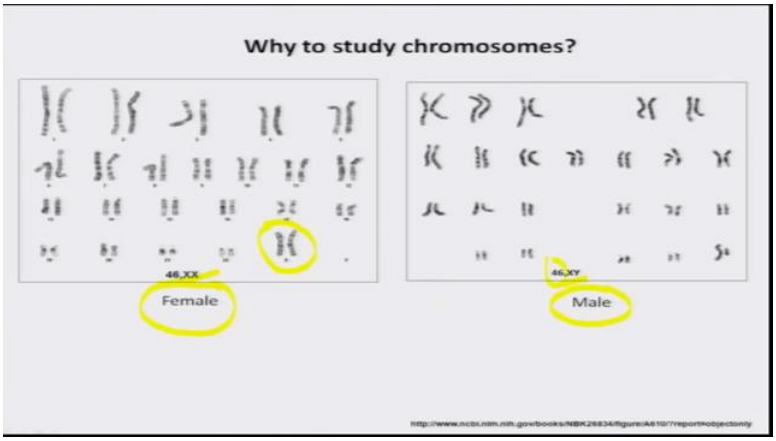

So, that is what we have said. So, we have the karyotype which you can distinguish by looking at whether the karyotype belongs to a male or female. So, you call it as 46-XX, because that is normal 46 chromosomes. It is XX, because this particular pair has got two X chromosomes. Therefore, this karyotype is that of a female. This is male because XY, you have 46 chromosomes, but you have a pair of sex chromosome which are heteromorphic; one large X chromosome, one small Y chromosome. So, this represents a male. So, this is how you are able to distinguish the male and female karyotype. That is a classic method.

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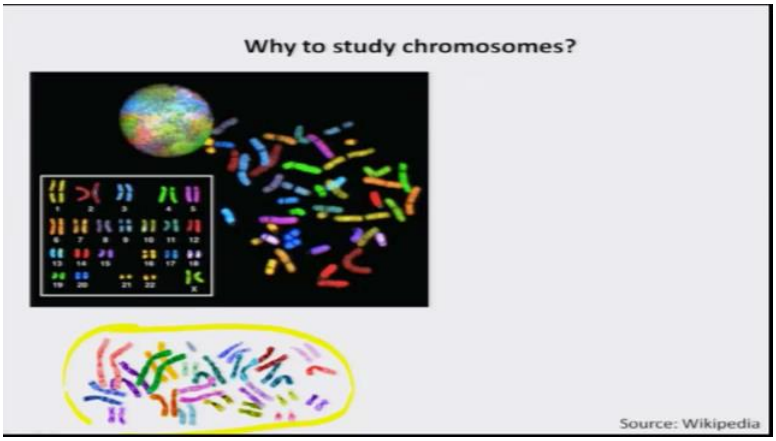

Now, you have very different sensitive methods by which you are able to identify each chromosome using different colours. That is called as spectral karyotyping. So, even in an image like this, you are able to identify for example, each pair of the chromosome and easily you can sort them based on the colour which really helps us to robustly identify if there any changes in the chromosome, which will be talking.

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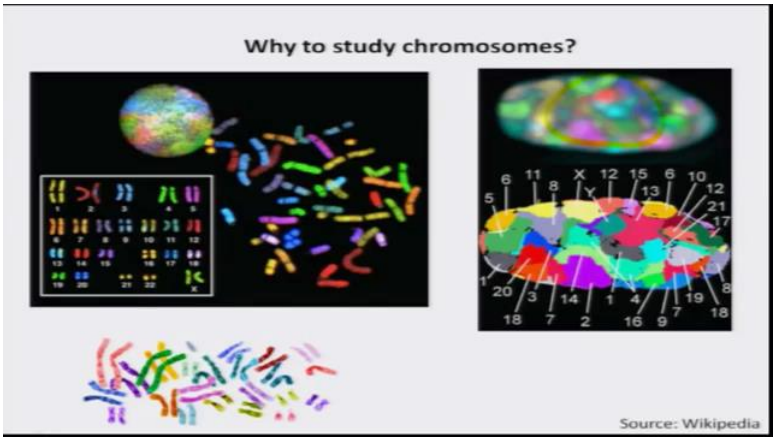

Now, this kind of approach also has helped us to understand that chromosomes are not randomly distributed in the nucleus. What is shown here is an interface nucleus, meaning this is a nucleus, wherein the chromosomes are active in the process of transcription. They are being copied to make RNA, the RNA is being copied to make proteins and so on. Even there, you see that each chromosome has domains particular region on which they are anchored and probably that has got some functional relevance. So, that is how the chromosomes, the study of chromosomes really helped us to understand how they function and how changes there may affect the cell normal function.

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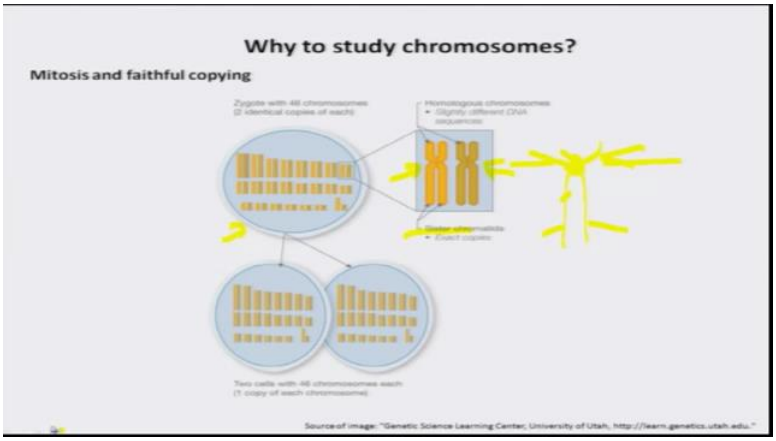

So, we can study the chromosomes in two different processes; one is meiosis, other one is mitosis. Mitosis is the, you know, copying process; all our cells when we grow, you know, cells divide and that is one of the way by which we are growing or when there is a wound or when there is a cut in your body, cells divide, multiply and the healing process also involves mitosis. In this process what happens? There is a copying of the DNA and, and exactly that is what you see here. So all of us are diploid, meaning two copies of all the chromosomes one that you derived from father, the other one that you derived from mother.

So, in this process what you are seeing here is that when you, when you make a metaphase spread, when you have arrested the cells at metaphase, then you make the spread of the chromosome, you would find this kind of structure, wherein you have the chromatid, which are attached around the centromeric region and each chromatid is called as sister chromatid, meaning they are exact copies. So, basically this chromosome that is on the left side is derived from one of your parent and this chromosome on the right side is derived from the other parent. So, these two chromatids are identical copies of the same chromosome and they are attached towards the centromere, because they are about to be pulled to the two daughter cells. Therefore, the metaphase chromosomes look like that. In fact, for any gene on a given chromosome, in this you would have four copies, right, because the cell is about to be divided.

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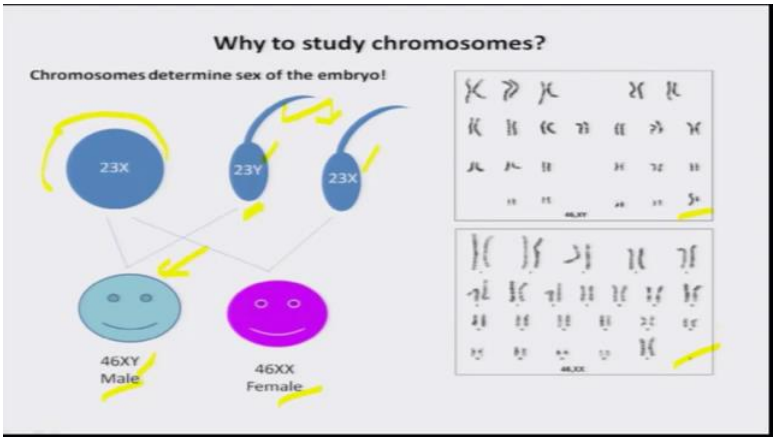

So, how do really chromosomes help, I mean, this help in determining the sex of the embryo? So, this X cell that you see here, the X cell is of one particular type, because invariably these are having X chromosome, because X is, two X is associated with female. So, any germ cell which gives rise to an egg would have 23 chromosomes, of which one would be the X chromosome. But, the males are capable of making two different types of sperms, because they are 46XY. So, they will have 23 chromosomes in each sperm, but 50% of the sperm would carry Y chromosome, 50% of them would carry X chromosome. So, it all depends on which sperm, whether it is Y bearing sperm or X bearing sperm which fertilize the egg. If it is Y, then that embryo, resulting embryo would become a male; if it is X, then the resulting embryo would become a female. As a result, we are able to find and make the karyotype as you see here, 46XY or 46XX.

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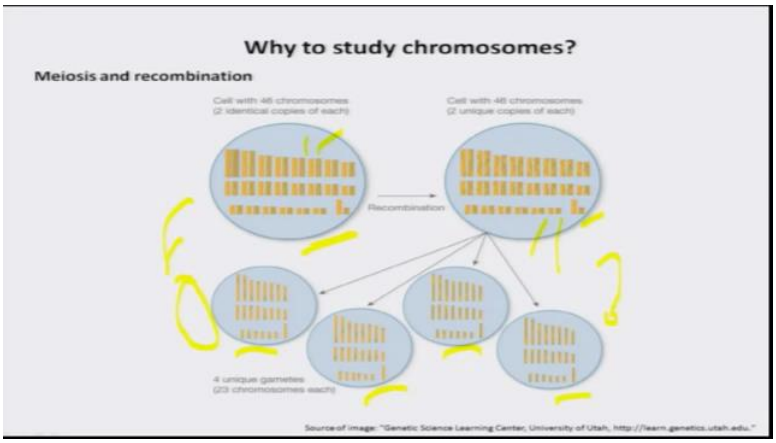

This happens during meiosis, meaning the process wherein, the cell division process where the germ cells are being made. So, the meiosis is a very complex and very important cell

division process that takes place in your germ cells. It not only reduces the number of chromosomes making what is called as haploid germ cells, having 23 chromosomes, but it also helps in the recombination, meaning as you can see here, these are the cells wherein you have the two chromosome, one pair, meaning the one that you got from mother and father, but in the meiotic cell what happens is that there are exchanges that take place between the paternal or the chromosome derived from father and mother and not only such kind of shuffling takes place and each of this are sorted into different combinations in the germ cells.

In other words it is like putting all together, shuffling and sorting it in different germ cells. As a result, the resulting germ cell, each one of them would be very, very unique in terms of the combination of the DNA segment it has got. Here for example, you may have had more DNA that is coming from your father; here you may have more DNA that is coming from your mother and so on. So, that gives you the difference. Sometimes you know, your daughter may look more like your grandmother or grandfather. It may reflect the content of the DNA that was transmitted; as a result, they look very similar and so on. So, this process of recombination is very, very important for the variation that you see and the variations can be selected for one reason or the other. That is something that we discussed earlier.

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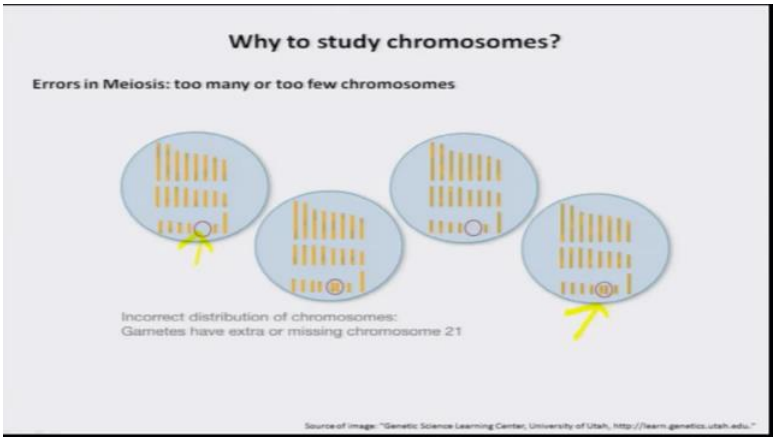

So, what we are going to discuss today or in this particular class is that how changes in the chromosome number may bring about some abnormality? So as I said, so during the meiotic process, the chromosomes are sorted into into different germ cells and when such kind of sorting takes place there is always a possibility that there are some errors. Fortunately, the errors are very, very minimal, extremely rare. Therefore, majority of the cell are normal, but

at times the error could be such that one of the resulting cell would not have a particular chromosome. It is one chromosome less or on the other hand, a particular cell may have more than one chromosome. It is 23 plus 1, 24 and such conditions if so happened that this particular germ cell led to the formation of the embryo, and then you may have different condition.

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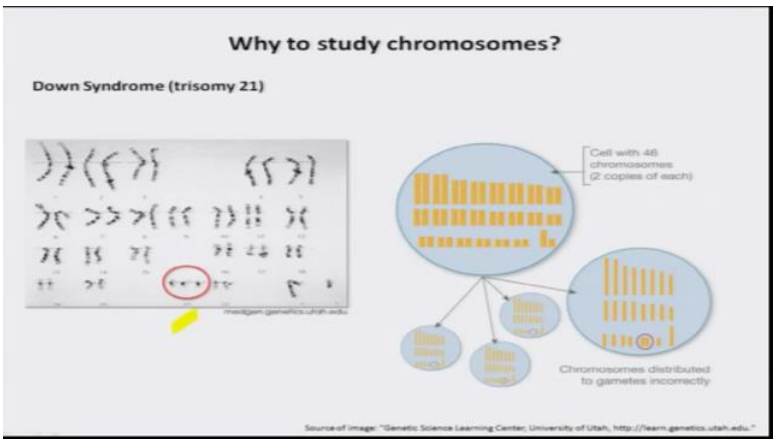

Majority of such conditions, wherein you have had increased number or decreased number, the embryo may not even survive. So, you may not even know when the embryo is conceived and is aborted. But, when the condition is not so severe, then the embryo can survive. Then you may have an individual who may have some phenotype, which is abnormal; example, one of them being Down syndrome which is resulting from three copies of chromosome number 21. This is a karyotype of an individual who show this particular syndrome. This is one of the common mental retardation syndromes, where the IQ, intellectual ability of the individual is very low. There are many, many congenital abnormalities in the development and this particular individual, the patient is fully dependent on somebody throughout his or her life span. So, this is one of the conditions, wherein you have three copies of the chromosomes resulting in a mental retardation. It could possibly mean that there was an error in the germ cell that led to this embryo and this individual. We will come to that little later; like as you see here there was a trouble.

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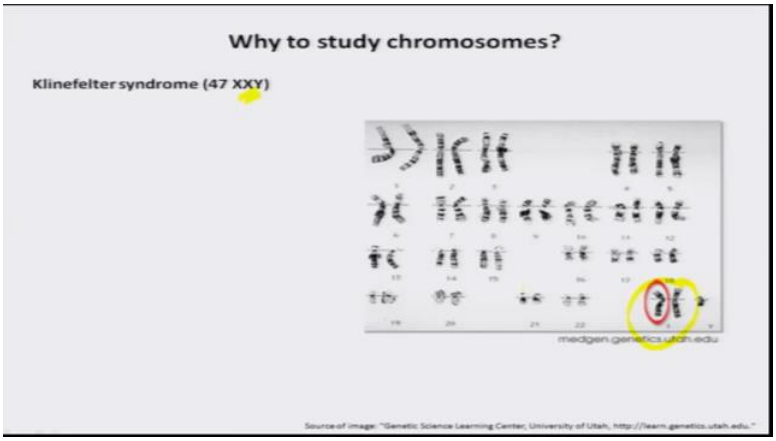

Now, there is another condition called Klinefelter syndrome. Again, here the individual is having one extra copy of the chromosome, but the extra copy is you have two X and one Y and he is male, because of the Y chromosome. But, this individual could be very tall, could have any behavioral problem and there are other issues as well. Again it is because of the extra chromosome. It should have been just one X and one Y, but due to some problem in the germ cell, this individual is having two X and Y, either because the mother has contributed both X chromosomes or the sperm has contributed both X and Y; both are possible.

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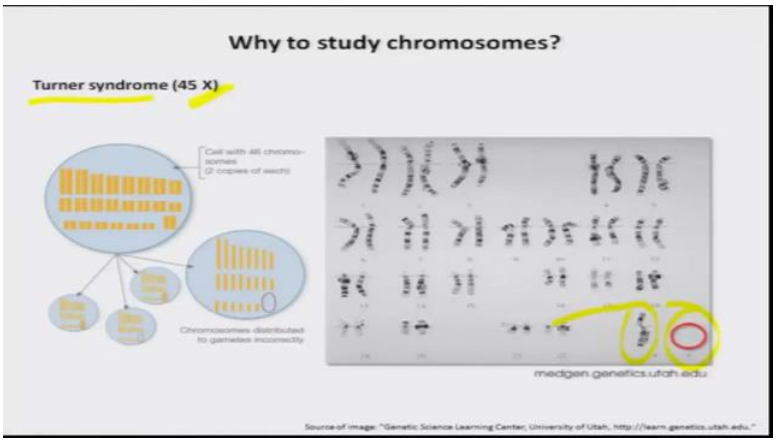

You could also have the opposite, meaning you have an individual who is having one chromosome less, 45 instead of 46 and has got only one X chromosome. As a result, it results in another condition called Turner Syndrome. Again, there are congenital issues, these individuals cannot be fertile and so on; they are not having a normal life. Again, because of absence of one sex chromosome, there is only one X; there is no X or Y. As a result there is no Y, as a result that individual developed like a female, but she may not be completely,

physiologically active as a female. Again this could result from a defect, wherein the sperm did not contribute X or Y or it could be a problem with egg cell itself. It did not contribute an X and what you had; also the sperm contributed an X and so on.

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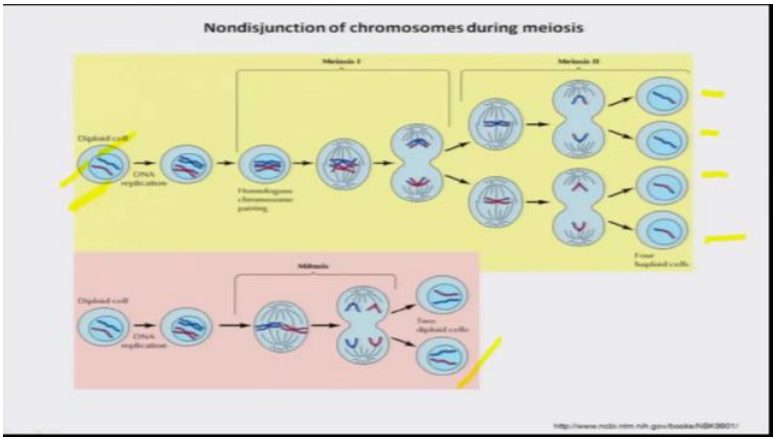

So, these are conditions, wherein you have a difference in the chromosome number; as a result you have a condition like Down syndrome, Turner or Klinefelter. So, let us look into what is the possible event or what is the possible error that led to such changes in the chromosome number? So, this happens because of a process called as nondisjunction, meaning these two, know, when the cells divide, the chromosomes are not sorted properly,? So, what is shown here on the top is a schematic of the meiosis, where the chromosomes are sorted into the germ cells, a reductional division.

What is shown below is mitosis, where it is a normal cell division, where there is no reduction, the 2n is maintained. This is a normal cell division. You can see that these are paternal, maternal chromosomes. Just one copy, one pair is being shown and you can see that, every daughter cell had one copy, one number, haploid as compared to its progenitor, which is diploid. So, that is how the germ cells become n, whereas in mitosis, the progenitor is also diploid and the resulting cell also is diploid.

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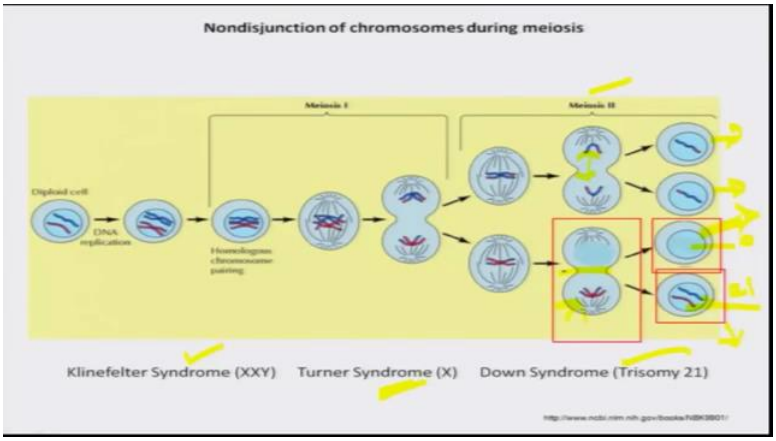

What happens in case of, for example Down syndrome or Klinefelter or Turner? Possibly this is what happens. For example, in meiosis II, when in a normal cell the two chromosomes are sorted to the pair, that is sorted to the two daughter cells which eventually form either the sperm or the egg, , it could so happen that in a cell, both copies are sorted to one of the two daughter cells. As a result, this particular cell is deficient for one chromosome and this particular cell has an addition of one copy. So, it has got two copies of chromosome, this has got zero copy of that chromosome.

So, if it could so happen that this is chromosome number 21 and if it becomes an egg and that fertilizes and becomes an embryo, that individual will be Down syndrome patient as like you see or it could be Klinefelter or on the other hand, if this particular egg cell resulted in an embryo, then that can become a Turner syndrome individual. So, depending on which chromosome is sorted the way shown here that is more than one copy is being sorted to the daughter cell, you may end up having different condition.

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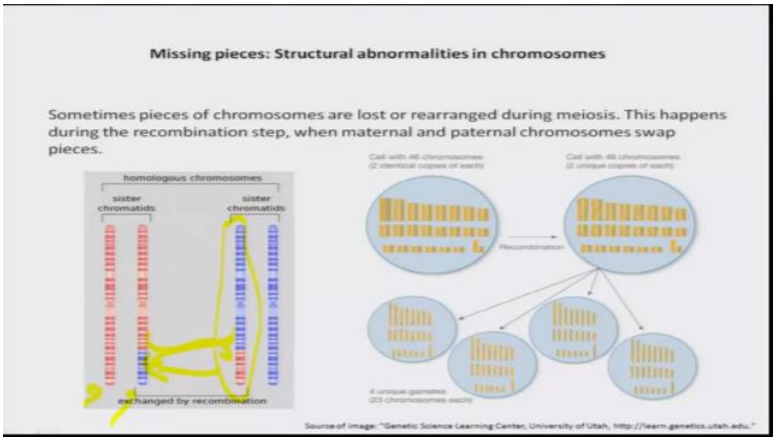

These are about the normal processes. So, what we have discussed is the whole chromosome being sorted into one or the other cell, wherein you have an addition or you have a loss of a whole chromosome; but at times you have had other problems. The chromosome number is similar, but may be a part of a chromosome is lost or duplicated or there are some other abnormalities, which is what we are going to see now in the next 10 minutes or so. So, what we need to understand is that during meiosis as we discussed, so you have the sister chromatids which undergo a process called as recombination.

In this a part of this come to this and a part of this goes here and this happens because of a precise DNA cutting; resulting in a double stranded break and the DNA is exchanged in such a precise way, even if the joining takes place in the middle of the gene, the reading frame is not altered. So, you have a perfect recombination, wherein you are able to recreate a new chromosome having part of chromosome that has come from father and part of the chromosome that has come from mother, but for the same chromosome. So, this brings in more variation. Now, such kind of recombination takes place in the mitotic cells. As is the case, when such recombination takes place, at times there could be error.

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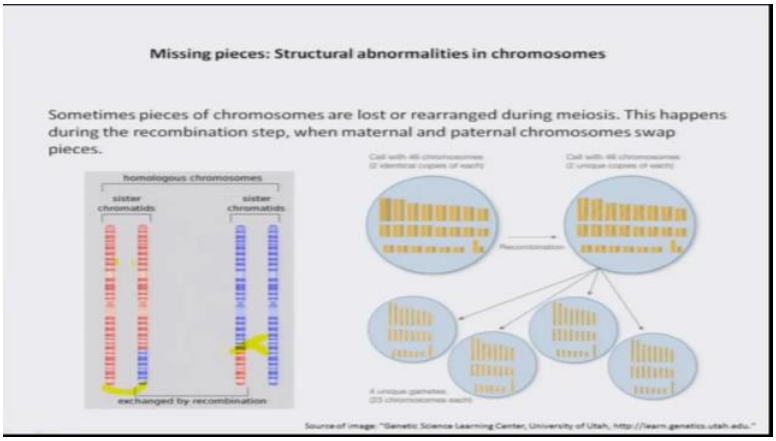

So, what we are looking at is that how changes within a chromosome or between two different chromosomes, which are not homologues, can result in abnormalities, which you call as structural abnormalities. These are like, a part of it is being lost or a part of it being duplicated or the order is changed; depending on how they affect the genes that are present within can result in one or the other condition. Most of such errors happen again during meiosis. Fortunately the frequency is extremely low, but it happens because there is an active process of recombination, wherein the two sister chromatids, the copies of the homologues, wherein there is an exchange like what is shown here. So, you have sister chromatids both representing the same chromosome, for example chromosome 1, there is an exchange between them. As a result, you have new combination that comes in. So, when these process happens, at times there are errors, wherein two different chromosomes can be fused together or two different regions of the same chromosomes can be fused together and that may result in conditions, where there is no difference in the total number of chromosomes.

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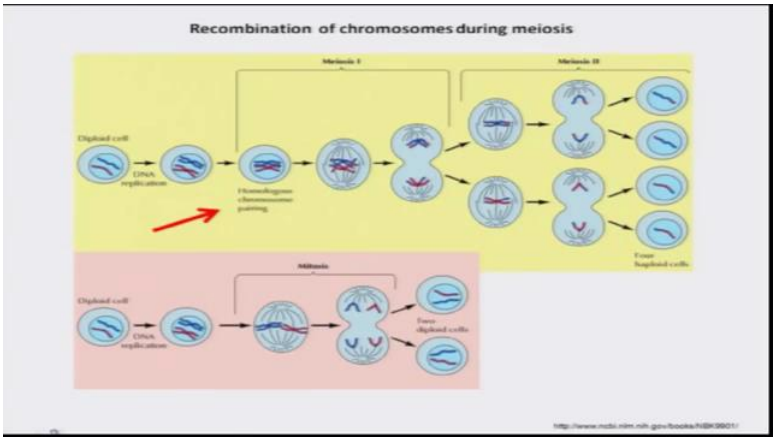

But, the way the chromosome is organized could be rearranged. So, this is what we have seen. What we have seen is that how a normal meiosis takes place and wherein you have a process the homologous chromosomes undergo recombination and there could be abnormalities here.

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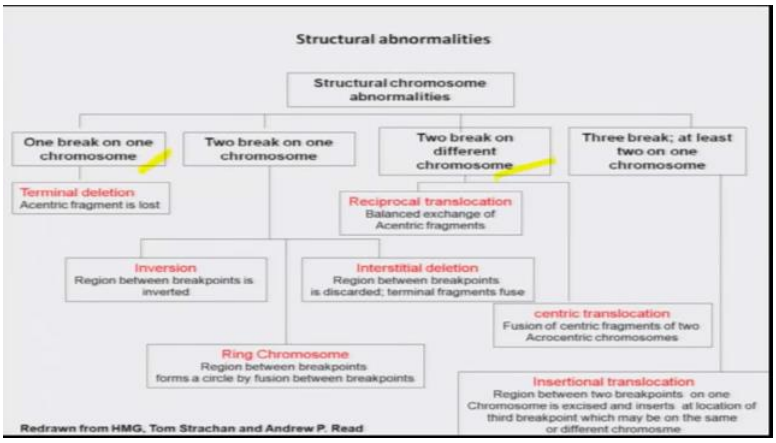

Such abnormalities are various types. It is a complex table. I will go through each one of them separately. So, what we are trying to say is that one group of them, is that, it happens on one particular chromosome or it can happen between two different chromosomes and depending on what kind of changes it happens, they are classified as different groups. We will see one after the other.

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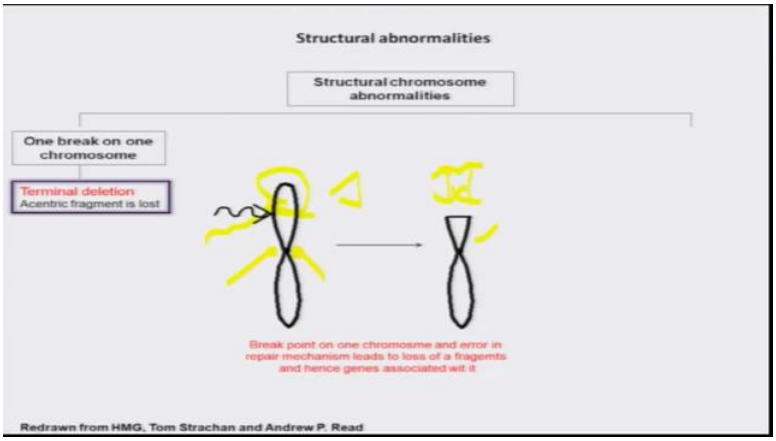

Let us look into the first one; that is one break on one chromosome, meaning a last, a particular region of the chromosome, something like here. So, the arrow here represents a mutational event which results in loss of this region of the chromosome and this chromosome has lost this region. Now, whatever genes that are present over there is lost, because this cannot be retained in the cell, because it doesn't have the centromeric region, because this is where your spindle binds and if this is, the last region is here, it cannot bind to the spindle and get copied and so on. So, you may have a cell in which one of the copies of the chromosome do not have this region of the chromosome which may have several genes. As a result, the cell is unable to function properly; the individual is unable to function properly.

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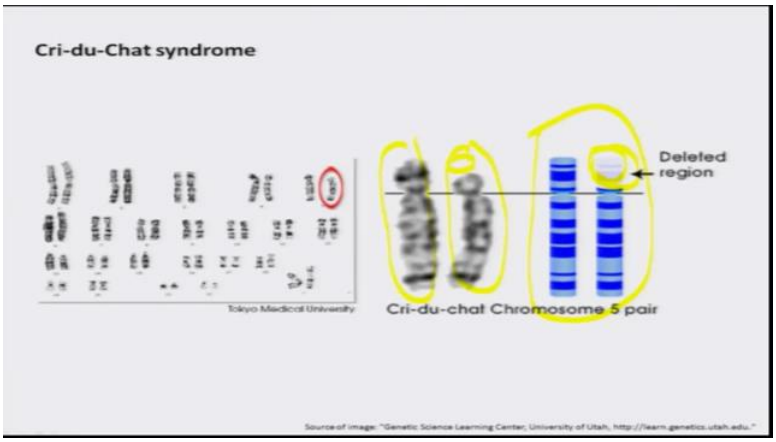

An example of that is the condition called cri-du-chat syndrome, which is a congenital condition where the babies, the way they make the sound look like or sound like a cat, the crying and so on. So, that is one of the reasons why it is called as cri-du-chat syndrome, but they have many congenital anomalies, the way the organs are developed and so on. It

happens because of chromosome 5, lost the upper portion of its chromosome and individuals are like here; they have one normal chromosome, but from the other copy, a part of it is lost. As a result, you have this condition.

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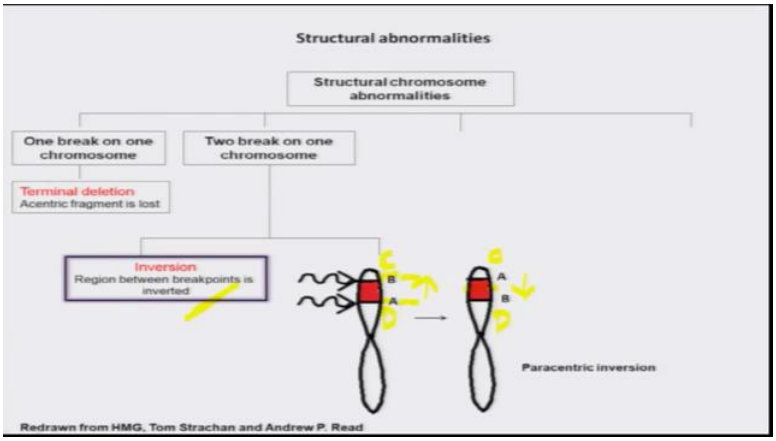

That is an example of terminal deletion wherein part of it, the upper or lower part of the chromosome being lost. So, you may have a condition, wherein there is no loss or gain in the chromosome, but the order of the chromosome or part of the region is altered like what you see here. So, there may be breakage here and here and if this is the orientation of this segment that gets inverted here. So you have a chromosome now which is different structure with reference to, for example this is C, this is D; originally B with C and A was with T, but now the position is altered. It might affect the way the genes that are present in this region are functioning. So, you end up having some condition which may affect the individual. So, that happens because of inversion. Here, the breakage happens at two places, but within the same chromosome and therefore it is called as inversion.

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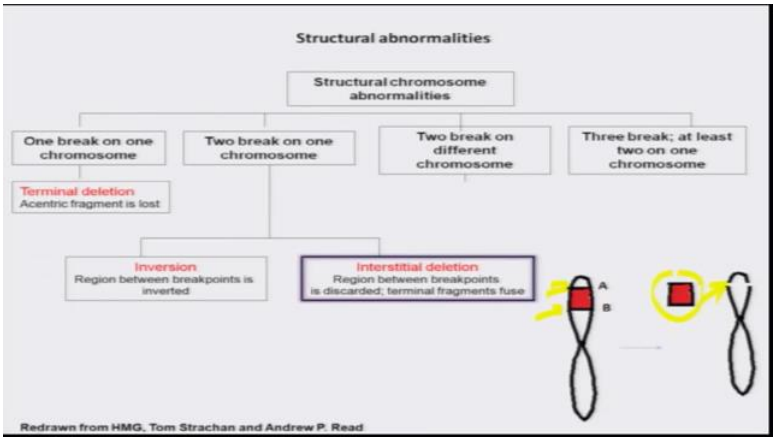

Again there could be condition, wherein there is breakage that happens in two places of chromosome. As a result, you have a fragment that comes out of the chromosome, and, may go and integrate into some other region of the chromosome and that may end up in some conditions because of increase in the copy number, or the way the genes function is altered and depending on what conditions you are looking at.

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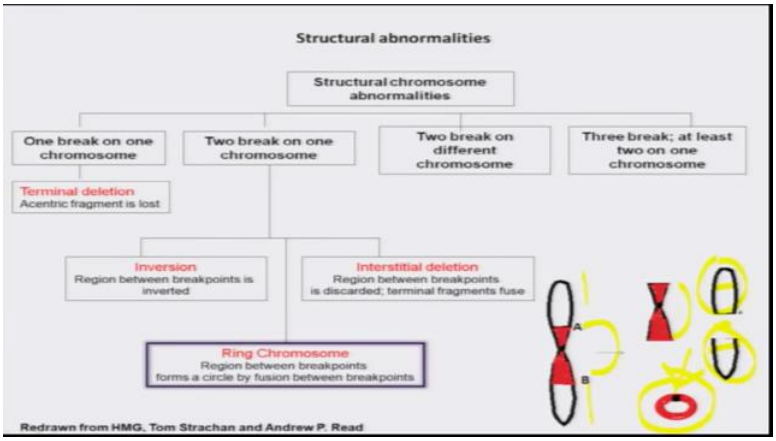

There are also conditions wherein two breaks in a chromosome, can result in very abnormal structure which is called as ring chromosome, meaning they have lost the telomere, this part and this part and the A and B join together to form as a ring chromosome; then they can survive, because still they can bind to spindle and being separated to the daughter cells, whereas the other part is lost from the cell and this condition again, can have very, very severe consequence on the cell, because genes that are present here may be lost and such fusion can also activate certain genes and so on. So, again these are examples as to how different structures can alter the way the chromosome functions.

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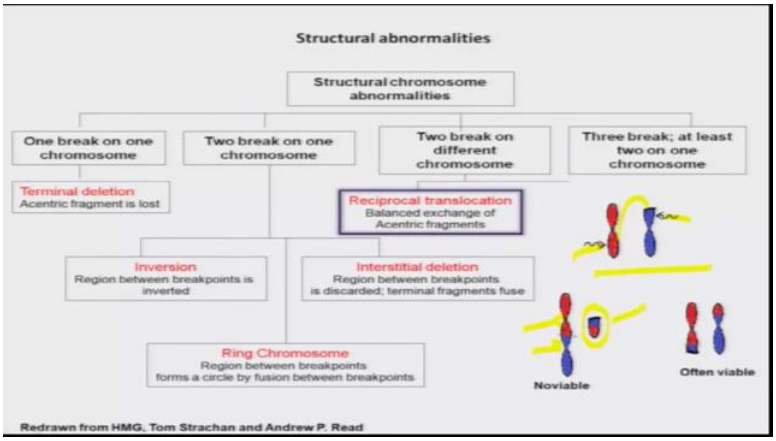

Now, we are going to talk about conditions where there are two breaks, but on two different chromosomes like that is shown here. There is a breakage here, there is a breakage here. Now, what happens as a result, now these two chromosomes join together like what you see here. There are two centromeres, this is last cannot survive the cell division, know and such events really, really affect the way the genes function and these are rarity. You may see it in certain cell lines and so on, but it would be very difficult to see it in individual, because such abnormalities are very, very lethal and the embryos even don't survive. But such, know, conditions are seen in individuals; there may be few cells that carry that.

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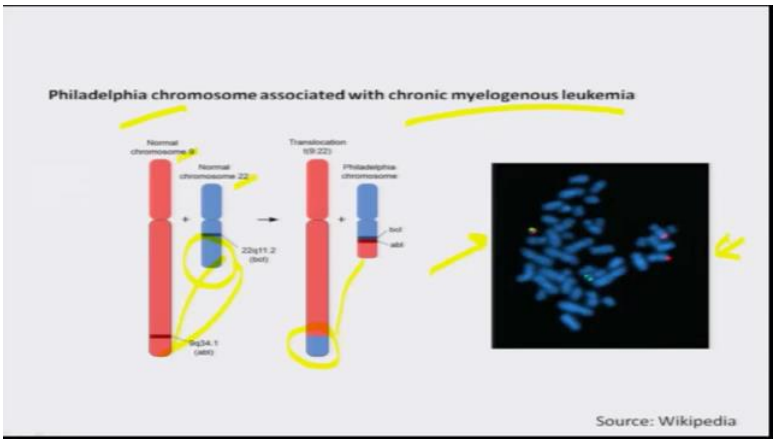

One of the classic examples of chromosomal translocation, a region of the chromosome going and joining elsewhere is represented by the so called Philadelphia chromosome. This is one

common rearrangement between chromosome 9 and chromosome 22, wherein a part of chromosome 22 gets translocated to chromosome 9. This is called as reciprocal, meaning a part goes to this and other part comes here. So, this result in a very chronic condition called the blood cancer or leukemia and this is often detected using this kind of staining on the chromosomes. So, this is one of the diagnostic features even to identify whether a person is having this particular cancer or not. But, these are recurrent event, often people see this.

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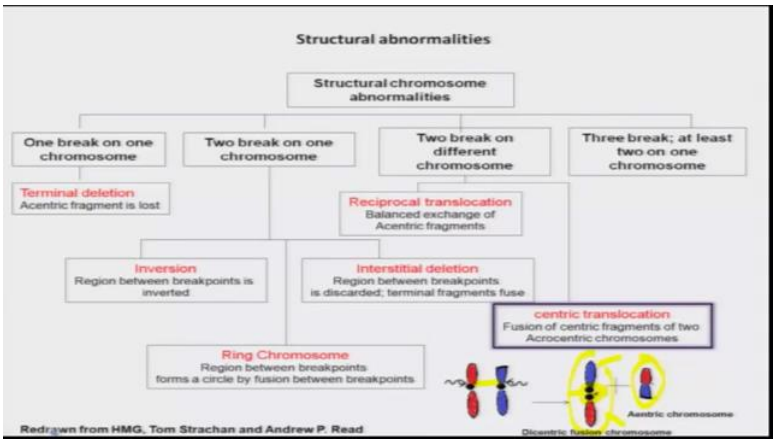

There are other conditions, wherein you have, as shown here, two different chromosomes involving around the centromeric region, can fuse together to have two different halves of the chromosome as one and other regions are lost. These are called as the dicentric fusions depending on how they fuse together. But normally, the fusion happens near the centromere. Again, these conditions are not really stable; we don't see it in individuals.

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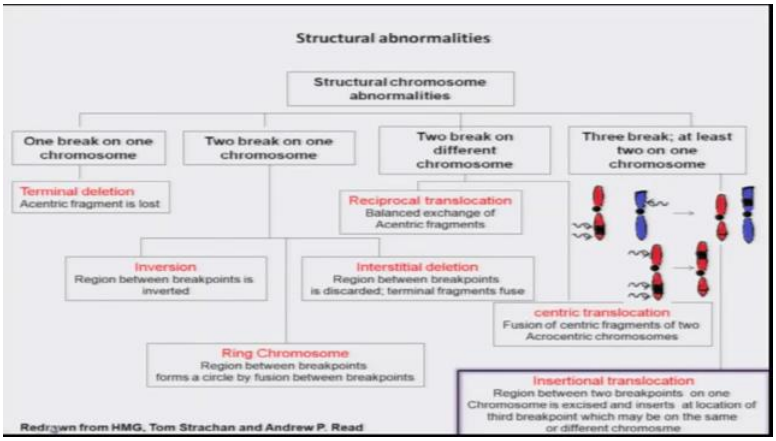

So, these are some of the examples how breakage in the chromosomes can alter the way they are arranged and majority of such changes, translocations and exchange of the chromosomes are seen in conditions where either i it is the consequence of some cancerous event or it could be the cause of the event.

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This particular slide gives an example as to how in different conditions of cancer you have translocations involving various chromosomes. So, that gives an example as to how different structural abnormalities either cause or are associated with several conditions.

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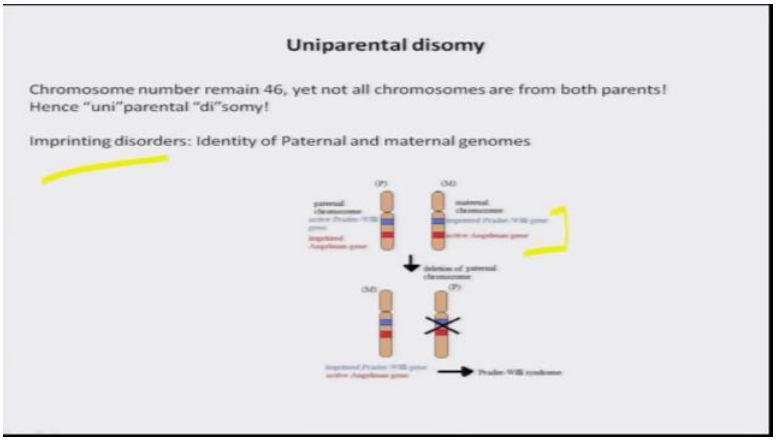

Now, we are going to the last section; we are going to look into unique condition called Uniparental disomy. What does it mean? Here, in this condition, the chromosome the number remains 46. If you do a karyotype, the individual is perfectly normal. He or she has got the required number of the chromosomes. There is no gross change in the chromosome, they all look normal. But, only difference is that not all chromosomes are from both parents. All of us has got one of the two, in each pair one chromosome come from father, the other one has come from mother, but in these individuals may be there could be one chromosome which has come from only one of the parents, the contribution from the other is missing. Therefore, it is called as uniparental, meaning from one parent, disomy, because otherwise you are diploid when you look into the number of chromosomes and such conditions are associated with a large number of cancers, which happens either because of non disjunction again or it could be somatic, meaning it happens only in certain tissues in your body not really gifted by your parents.

But, the importance of such contribution that you should have the chromosomes derived from father and the mother, have come from our understanding on a unique group of disorders called imprinting disorders. In this condition, what we know is there are genes which are expressed only if that particular gene copy is derived from father or there are genes that are expressed only if that gene copy is derived from mother. So, these are called as imprinted genes. So, if I have uniparental disomy for a particular region of a chromosome or a particular chromosome, then if that is derived from my mother, those genes that should be expressed if it is derived from father, these genes will not be expressed.

As a result, I am equivalent to not having these genes and I may end up having a particular disorder and what is shown here is the two sister disorders called as Prader - Willi syndrome and Angelman syndrome are classic examples of imprinting disorders, wherein they show parent specific expression pattern, whether the alleles are derived from father or mother and when you have such Uniparental disomy, either you don't express the set of genes that should be expressed in your paternal allele or that are expressed from maternal allele. So, you may want to go and read more on that, because it is a very complex genetic control. There are good reading materials available in the paper, in the book that we have recommended for this course and if there are any queries you can write to our teaching assistant. They will be able to help you and that is pretty much the lecture for the first week, wherein we tried to introduce what is central dogma, how the information is processed and how defects there might affect the way the genes function and beyond regions of genes, we have looked at how gross chromosomal changes, either addition or loss of chromosome, can affect and even within a chromosome or between chromosomes, how the structures may alter and may associate with one or the other forms of the disease. So, that pretty much ends the first week lectures on this particular course; we will meet you again next week.