X CHROMOSOME INACTIVATION

1. Hello, welcome to Introduction to human genetics. This is the third lecture on human cytogenetics, where we are going to continue discussing human sex chromosomes, paying special attention to X chromosome inactivation phenomenon.

2. As you remember from the previous lecture, sex chromosomes, X and Y, are heteromorphic- they differ in size and gene content.

3. Presence of two X chromosomes in normal human females and only one X chromosome in normal human males is unique compared with the equal numbers of autosomes present in the cells of both sexes.

4. Since females carry two X chromosomes, they have two copies of all the genes on that chromosome, while XY males have only one copy of all the genes on the X chromosome. In other words females have twice as much doses of each gene on the X chromosome as males. If the two copies of the gene were expressed at the same level from each X chromosome, females would have twice as much of each protein product encoded by genes on the X chromosome. In fact, for all X chromosome gene products that have been tested: the amount of encoded protein is the same in males and females. How does this happen? Well, the amount of X chromosome gene products in both sexes is equalized by a process called dosage compensation.

5. In the previous lecture I showed you that the fertilized egg is determined to be male or female depending on the sex chromosome contributed by the sperm. If a sperm with an X chromosome fertilizes an ovum, the zygote is female. In such a case one chromosome X is of maternal origin, and the other is of paternal origin. In humans, these both X chromosomes are genetically active in female zygotes and all cells of early XX embryos. Then, early in the development, at the stage of over 32 cells each cell picks the random X to inactivate. Some will choose the X chromosome from the mother, and some will inactivate X chromosome from the father. For each cell, it is random whether the paternal X or maternal X is inactivated, but the choice is fixed for all subsequent descendants of that cell in the developing foetus and these chromosomes remain inactivated throughout life.

6. So, because of X inactivation every woman is a mosaic of cell lines with different active X chromosome.

7. The inactive X remains condensed during most of interphase and is visible in a variable proportion of the nuclei in most tissues as a densely stained mass of chromatin known as the Barr body or sex chromatin.

8. An excellent example of the mosaicism in mammalian females are tortoiseshell cats. In cats, an X-linked gene for coat colour has two alleles: one produces orange coloured fur, and the other produces black fur. So in the heterozygous females you will see patches of orange fur mixed with patches of black fur. Such X-linked coat colour patterns do not occur in male cats because all their cells contain the single maternal X chromosome and are therefore hemizygous for only one X-linked coat colour allele. And for that reason male cats would be either all orange or all black.

9. It is hard to see patchy pattern of X chromosome inactivation in normal women. However a rare X-linked recessive disorder, hypohidrotic ectodermal dysplasia may serve us as an interesting example. Males hemizygous for this disorder show absence of teeth, sparse hair growth, and lack of sweat glands.

10. The skin of females heterozygous for HED reveals random patterns of tissue with and without sweat glands. The locations vary from female to female, based on random pattern of X chromosome inactivation during early development.