

Mosaicism

Genes are instructions that control the way we grow and develop. We have about 20,000 different genes. We have two copies of each gene. We get one copy of each gene from our mother and one copy from our father and pass one copy onto each child.

Every time a cell divides all the genes are copied out. Sometime copying mistakes happen and we know that we all have changes in many genes. Sometimes these changes have come from one of our parents and sometimes the changes happen just in us.

What is mosaicism?

Mosaicism is the term used when someone has a mixture of cells – some of the cells have a gene change and some do not.

This is illustrated by these diagrams:

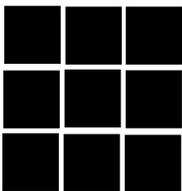


A cell with two normal copies of a gene

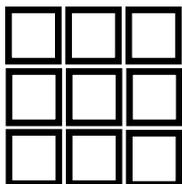


A cell with one normal and one altered copy of a gene

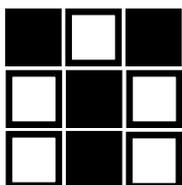
Someone with normal genes will have this pattern of cells



Someone with a genetic change in one copy of a gene in every cell in their body will have this pattern of cells

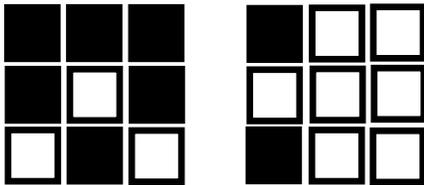


Someone who is mosaic for a change in a gene will have this pattern of cells. You can see why it is called mosaicism as it looks like a mosaic.



The proportions of cells will vary from person to person. Some people will have high numbers of cells with normal genes and some people will have high number of cells with altered genes. Everyone is different.

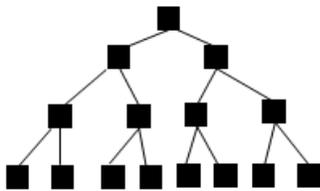
The pattern of cells with normal genes and cells with altered genes can be different in different parts of the same person. This means that someone might have a lot of cells with normal genes and not many cells with an altered gene in one part of their body, but a lot of cells with an altered gene and not many cells with normal genes in another part of their body. Again, everyone is different.



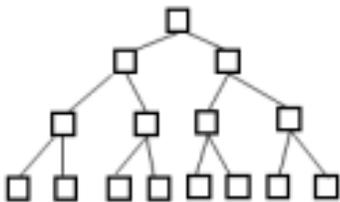
How does mosaicism happen?

We all start as one cell, which is formed when an egg and sperm cell fuse together at conception.

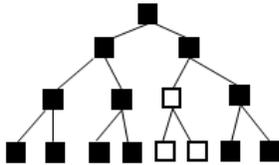
That cell divides into two cells, and each of those cells divide into two. This happens millions of times until a baby is fully grown and continues to happen in many cells throughout of life. This is shown in this diagram:



If an egg or sperm has a genetic change this will be passed to a baby and will then be present in every cell of the baby. Sometimes a gene change happens at the moment of conception and, again, that change will be present in every cell of a baby.



But sometimes a change in a gene happens after conception. It will then be present in every cell that comes from the cell where the change started, but won't be present in other cells. This is what causes mosaicism.



A change in a gene happens by chance and we all have many of them. The changes are not caused by anything that happens in a pregnancy and are no-one's fault. Most of them do not have any effects at all

Generally, if a gene change happens soon after conception, the change will be in a lot of cells throughout the body. If the gene change happens later in development then it will be in fewer cells and may only be present in one part of the body. The proportions of cells with normal genes or the altered gene may be different in different parts of the body. Everyone is different, both in the balance of normal and altered genes and the balance in different parts of the body.

Mosaicism happens often in nature and explains why different colour leaves can happen on the same plant and why some animals can have patterns on their coats, like a tabby cat.

Genetics of retinoblastoma

Everyone has two copies of the retinoblastoma (RB) gene. A retinoblastoma tumour develops when both copies of the RB gene in the same cell are altered.

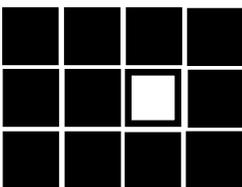
People who have the genetic form of retinoblastoma have a change in one copy of the RB gene in every cell. A retinoblastoma develops if a change develops in the other copy of the gene in a cell of the eye. If this second change happens only in one cell they will develop unilateral retinoblastoma. If this change happens in more than one cell, they will develop bilateral retinoblastoma.

People who have the non-genetic form of retinoblastoma are born with normal copies of the gene in all their cells. They develop changes in both copies of the RB gene in one cell in the eye so will only develop unilateral retinoblastoma.

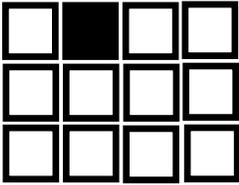
Is mosaicism tested for when genetic tests are done for retinoblastoma?

Yes. The routine tests will detect most cases of mosaicism. But they may not detect it if the proportion of cells is quite unbalanced and more than 90% of cells are one type with fewer than 10% of the other type. This means that:

- No genetic change may be found in people with high numbers of cells with two normal genes:



- Only the genetic change may be found in people with high numbers of cells with an altered gene:



Because we know that genetic testing might not detect all cases of mosaicism, we are quite careful in interpreting results. This is why we say to some families that the results are normal but any new babies in the family should still have eye checks.

Why is mosaicism relevant to retinoblastoma?

There are three things to think about with respect to mosaicism and retinoblastoma. These are:

- The chances of a child developing retinoblastoma
- The chances of passing an altered RB gene to a child
- The chances of developing a second tumour

What are the chances of someone with mosaicism developing retinoblastoma?

It is impossible to give an accurate answer to this as the chances will be affected by the level of altered genes in the eye. We usually test genes in blood. We can occasionally test other tissues but we cannot test the genes in an eye, unless the eye has been removed. The balance of normal genes and altered genes in the eye may not be the same as that in the blood.

Some people with mosaic changes in the RB gene will develop retinoblastoma but some will not. We cannot give precise chances for this, but the chances will be smaller than for someone who has a genetic change in every cell.

Sometimes we find a mosaic gene change in someone who has retinoblastoma. In that situation, the gene change will be linked with the retinoblastoma.

Sometimes we find a mosaic gene change in the parent of a child with genetic retinoblastoma. In that case we can be sure that the parent will not develop retinoblastoma, but there is a chance that they would pass the altered gene to a child.

It would be extremely rare to find a mosaic change in the RB gene in a child who did not have retinoblastoma as a mosaic change is not inherited from a parent and we would have no reason to test a child.

What are the chances of someone with a mosaic RB gene change passing the altered RB gene to a child?

Again, it is impossible to give an accurate answer to this as the chances will be affected by the level of altered genes in the ovaries or testes, where the eggs and sperm are made. We cannot

test the genes in the ovaries and testes and the balance of normal genes and altered genes in the eye may not be the same as that in the blood.

This means that anyone who is found to have a mosaic gene change will have a chance of passing on the altered gene to a child. Again, the chances will be smaller than for someone who has a genetic change in every cell.

Accurate genetic testing will be possible for the children of anyone who has a mosaic change in the RB gene. The testing can be done after a baby is born, in pregnancy or using preimplantation genetic diagnosis, in exactly the same way as for anyone who has a gene change in every cell.

What are the chances of someone with a mosaic RB gene change developing a second tumour?

Again, it is impossible to give an accurate answer to this as the chances will be affected by the level of altered genes all over the body and we cannot test for this.

Most people with a change in the RB gene do not develop second tumours. The chance of someone with a mosaic gene change will be smaller than for someone who has a genetic change in every cell.

Summary

Mosaicism for changes in the RB gene is relatively rare and is only relevant for a few families.

It can cause some people to develop retinoblastoma.

It can mean that some families have a chance of having more than one child with retinoblastoma.

It is routinely tested for and if a mosaic change in the RB gene is found in a family, the results will be discussed with that family.

Elisabeth Rosser 2017