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What is genetic mosaicism and how can we use its underlying principles in new treatment and diagnostics?

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Introduction

Genetic Mosaicism is an existing series of genetic traits through mutations with having two or more genetically different somatic cells1. Sometimes genetic mosaicism can be hereditary, but generally the mutations occur throughout development. Early studies involving Drosophila Melanogaster (used as a genetic studies model organism today) revealed the foundations of genetic mutations, discovering “mutant” types with white eyes compared to the “wild”- type” with red eyes.

These early discoveries laid the basic principles of genetic mosaicism, with it being two or more different genotypes contributing to mutations and variations amongst organisms. Females within a variety of species are naturally biological mosaics due to X-chromosome inactivation3. In each cell, one of the X-chromosomes is “switched-off”, contributing to variation across populations. A prime example that can be observed within organisms is the tortoiseshell or the calico cat, which appears with multi-coloured pigmentation/patterning of their fur (refer to fig. 2).

Since males have only one X chromosome generally, male cats will express only one of these alleles hence will only exhibit one of the colours, however in some circumstances may differ (ginger or black)4. Our pigmentation is not affected in this way, but the phenomenon contributes to diverse phenotypes within females. Males do not have the switching-off of X-chromosomes, unless the male has more than one copy of the X-chromosome such as with Klinefelter syndrome patients with XXY chromosomes (refer to fig. 1 and 3), however this remains unclear.

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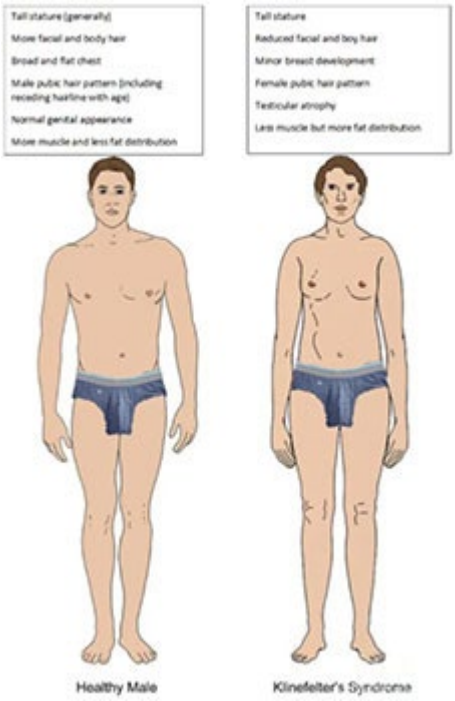

Fig 1. Traits of healthy males and Klinefelter males. Typical characteristics of the two groups are compared.

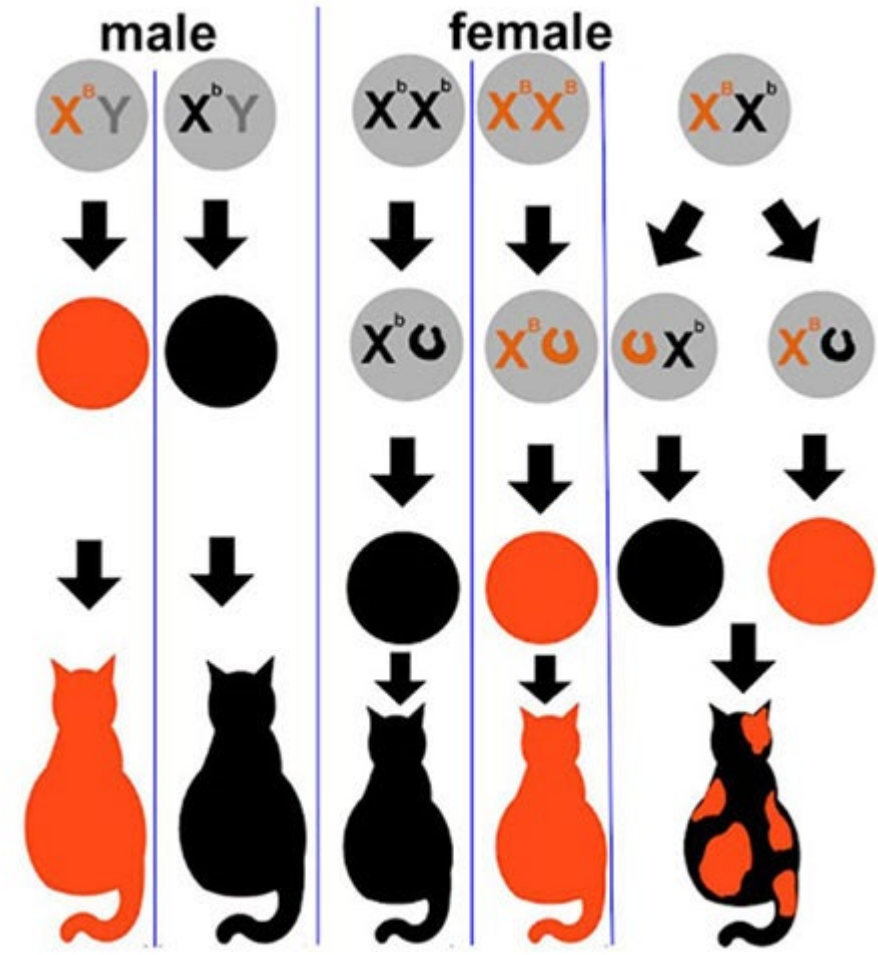

Fig 2. Calico cat X chromosome inactivation in males and females. Where XB and Xb indicate fur colour (seen on the X chromosome), the Y chromosome as seen in males does not contribute to fur colour. A barre-body (uncoiled chromosome) is shown in the randomly inactivated X-chromosomes.

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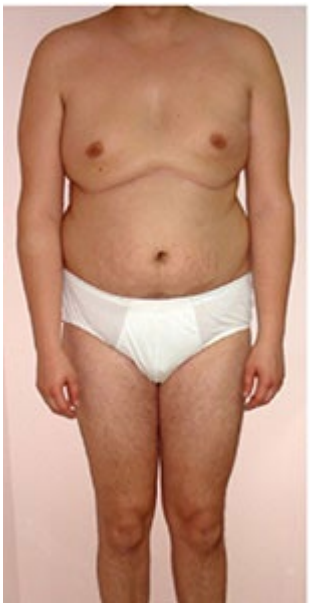

Fig 3. Kleinfelter syndrome in males. The stature of a typical Klinefelter syndrome patient is displayed.

Mosaicism types

There are a few types of Genetic Mosaicism such as mosaic monosomy/trisomy, germline mosaicism, and various other types6. Genetic Mosaicism is an important biological aspect in the treatment of diseases, for example, in trisomy and monosomy conditions, like mosaic trisomy 9 or mild Down's Syndrome.

Mosaicism types: Somatic Mosaicism vs Germline Mosaicism

Somatic mosaicism cells with more than one genotype and other categories of mosaicism can fall under this broad category7. A common group of diseases which can arise from somatic mosaicism is cancer. Germline mosaicism, on the other hand, is the mutation being carried within the gametes (before fertilisation). Some gametes will remain normal within the individual, but some will contain the mutation, due to the mutation in the stem cell early on. Germline mosaicism can be hereditary and passed down through generations, which is key in our understanding of genetic disorders6. An example of a condition caused by Germline Mosaicism is Haemophilia A and Haemophilia B, which are both X-linked disorders resulting in blood clotting abnormalities.

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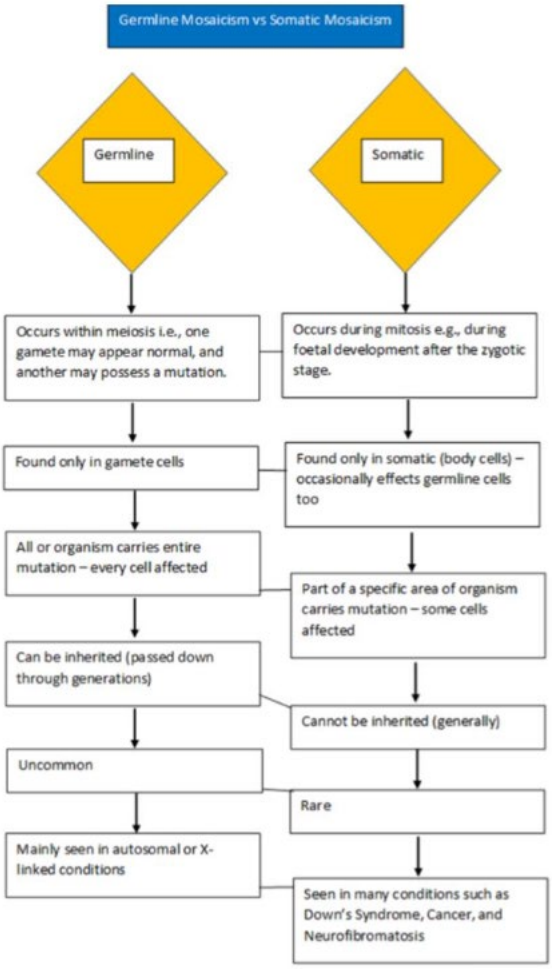

Fig 4. Characteristics of Germline and Somatic Mosaicism. Flow chart shows the comparison of the mode of occurrence (meiosis and mitosis), cells and localities affected, inheritance, commonality, and conditions under the categories.

Mosaicism types: Mosaic monosomy and trisomy

Mosaic monosomy/trisomy is when a mutation occurs during development., Causing some chromosomes to be affected by having two or more copies within the foetus, such as some forms of intersex, where the biological sex has both male and female characteristics9. Intersexuality is a trait typically observed in hornless goats. Mosaic trisomy is more common than mosaic monosomy and the conditions inherited are less fatal generally.

Within mosaic monosomy, the only existing condition where the foetus will survive as a result is Turner's Syndrome, however only a small proportion are genetic mosaics10. Many of the mosaic monosomy occur very rarely due to such abnormal nature and the severity of the conditions that arise; many developing embryos or foetus's do not survive. However, mosaic trisomy is a much more common appearance particularly trisomy 21 mosaics (Down's syndrome). The varying types of genetic mosaicism all generally appear very early on throughout development.

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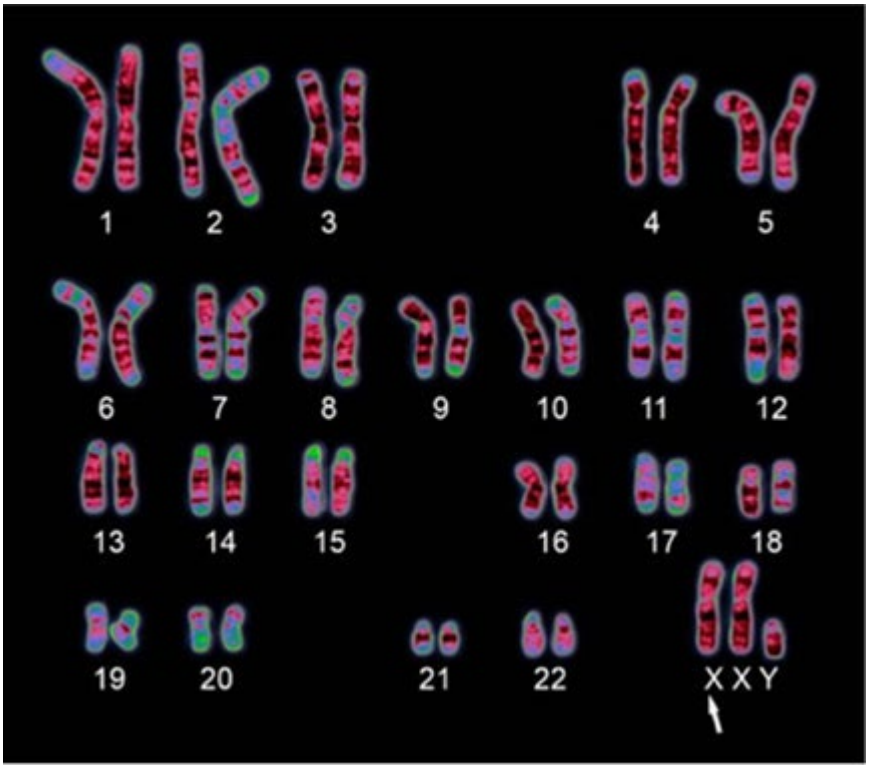

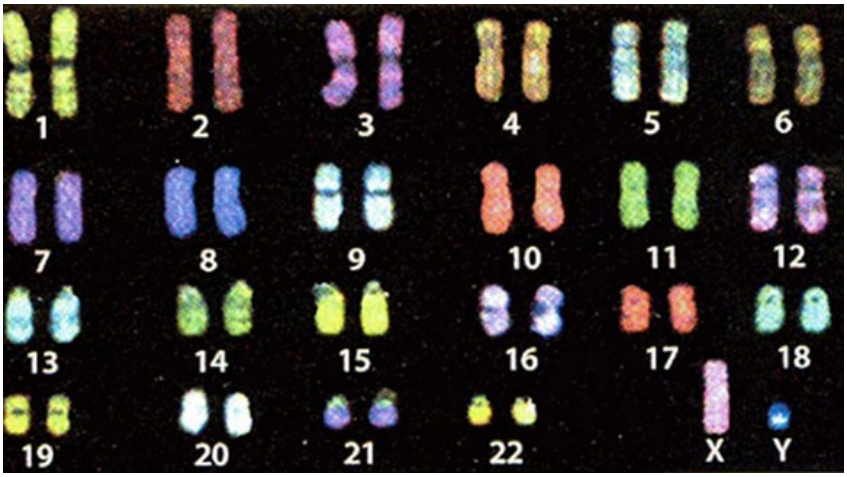

Fig 5. Karyotyping images visualised with fluorescent dyes. A displaying Klinefelter's syndrome (with the additional X chromosome} and B showing a healthy female's chromosomes.

Testing methods

Within modern day analysis of Genetic Mosaicism, testing methods include biopsies, chorionic villus sampling, amniocentesis, karyotyping, sanger sequencing, chromosome microarray and next-generation sequencing.

Testing methods: amniocentesis, chorionic villus sampling, and biopsies

During amniocentesis, amniotic fluid is obtained at 15 weeks or further during the pregnancy to avoid risk to the foetus11. The cells from within the fluid are then observed under the microscope for any abnormalities present. Further investigations will take place if the tissues appear abnormal, but this depends on why the testing is being done in the first instance. For example, if the cells appear crescent shaped when observed under the microscope then a sickle cell anaemia diagnosis is likely, but if this is not the case and the amniotic cells appear unusual then other testing follows as discussed below.

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Chorionic villus sampling is another prenatal diagnostic method, where a small amount of chorionic villus cells is taken using the guidance of an ultrasound and needle to penetrate through the skin into the womb12. However, the chorionic villus cells may be obtained slightly differently when inserting the needle into the cervix rather than through the skin. Often when the genetic mosaicism is complex, and amniocentesis is not suitable, then other testing methods are more suitable. Tissue samples may be obtained for analysis on neonatal (new-born) for examination, known as a biopsy13. A needle is inserted at the site of interest and the tissue is observed under a microscope for any abnormalities. Biopsies are common procedures for genetic disorders and other diseases too.

Testing methods: Karyotyping vs chromosome microarray

Karyotyping is a technique in which chromosomes are aligned and paired to detect extra copies, however the success rate of Genetic Mosaicism diagnosis through this method can be relatively low6. Samples can be taken from blood, bone marrow and may be commonly done alongside amniocentesis, mainly when testing for Down's syndrome. The cells taken within the sample are cultured and stained and observed at specific cell cycle stages. Sometimes chromosomes may not necessarily have an extra copy but may be abnormally shaped, combined with other chromosome numbers, have deletions/insertions, or be deformed. A prime example of a genetic condition is called Cri du chat which is extremely rare where the deletion of part of chromosome 5 is observed in patients14. Cri du chat mosaicism is an even rarer condition since around 3% of patients with the condition display genetic mosaicism15. Approximately 1 in 50, 000 are born with the condition, making the genetic mosaic proportion an incredibly infrequent.

Alternatively, chromosome microarray (CMA) is a much quicker technique since specific cell cycle checkpoints are not needed for this observation. CMA chips are labelled within the procedure and target specific chromosome loci for analysis. Samples are compared with healthy samples using the software input from a computer and then diagnosed.

Testing methods: Sanger Sequencing vs Next-Generation sequencing

Sanger Sequencing allows single nucleotides to be sequenced, often being useful within single-gene disorders such as autosomal dominant or x-linked (genetic disorders causing mosaicism)16. The technique can be very time consuming, and it could be more beneficial to use other techniques such as next-generation sequencing. Next-generation sequencing is a highly accurate method of detecting small changes within DNA. Deletions, insertions, and single nucleotide variants can be detected efficiently.

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