

Editorial

Genetic mosaicism

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A knowledge of mosaicism and the mechanisms involved is important in understanding the distribution of lesions in many skin diseases, particularly those with a genetic basis. Mosaicism refers to an organism having cells with a different genetic make-up adjacent to each other giving rise to a variety of patterns in the skin, particularly linear and segmental lesions. These clinical patterns have been described by Happle¹ as follows:

- Type 1a are lines of Blaschko with narrow bands. The representative disease is incontinentia pigmenti.
- Type 1b are lines of Blaschko with broad bands. The representative disorder is the McCune-Albright syndrome.
- Type 2 is the checkerboard pattern. An example would be a large generalized speckled lentiginous nevus or Becker's nevus.
- Type 3 is phylloid or leaf like pattern. An example would be phylloid hypomelanosis.
- Type 4 is the patchy pattern without any midline separation. An example would be a congenital giant melanocytic nevus.

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- Type 5 is lateralization. An example would be the CHILD syndrome.

The genetic mechanisms underlying mosaicism include those affecting germ cells, somatic cells and sometimes a combination of both.² It depends to some extent on when in the development of the embryo the mutation occurs. If it is very early on, before germ cell differentiation has occurred, then both germ cells and somatic cells may be involved, but if after the thousand cell stage, it can be one or the other.

Blaschko's lines are probably the commonest examples of mosaicism that we see because they involve cells of the epidermis.³ The cells of the epidermis originate from the neural crest and in the developing fetus they grow out laterally. However, as the fetus bends and unfolds, so these originally straight lines start to assume the shape of a fountain or volcano and hence give the characteristic patterns we are all aware of.

The genetic causes of mosaicism are described as follows:

1. Half chromatid mutation
2. Lyonization
3. Post zygotic mutation
4. Chromosomal non-disjunction
5. Chimerism

To deal with each of these in turn, a half chromatid mutation is a defect in the formation of DNA during the first meiotic division of gametogenesis where one strand of the double strands of DNA carries a mutation. The phenomenon of semi conservative replication within the zygote or fertilised egg gives rise in one of the daughter cells to a complete point mutation, usually a wrong base pair amino acid. If this half chromatid mutation has occurred in the gamete then mosaicism will already be present at the two cell stage, hence epidermal nevi or nevoid like disorders in the epidermis that are bilateral and widely spread may be explained by this mechanism although a very early post-zygotic mutation, after fertilization has taken place in the early four or eight cell stage, can also give rise to this pattern.

Lyonization refers to the X chromosomes. In females where there are two X chromosomes, one of them is inactivated at a very early stage and becomes what is known as a Barr body. This occurs in all women. The X chromosome that is inactivated may have come from the child's mother or from the child's father but once this inactivation has occurred it is the same in all daughter cells derived from it. Hence, if there is a disorder carried on an X chromosome from one of the parents, it will only be expressed in some of the cells. Again because of the randomization process, this is likely to be a widespread epidermal nevus type disorder rather than a small localized area. A post-zygotic mutation is a mutation occurring after fertilization and the initial multicell stages of the embryo. If it occurs early in the multicell stage formation then the condition will be widespread. If it

occurs later then it may well be localized, either linear, segmental or one of the other clinical patterns described by Happle.¹

Chromosomal non dysjunction is the failure of chromosomes to separate correctly during either meiosis or mitosis giving variations in chromosomal numbers or structures e.g. trisomy or translocations. These may occur early or late. Chimerism is where an organism has two very genetically distinct cell populations either due to fertilization of one egg by two sperms or fusion of two fertilised eggs. Hence, the mosaicism is due to two different genetic organisms with two different cell lines.

The patterns of cutaneous mosaicism will also vary according to the cell type involved. Involvement of epidermal cells gives rise to the classic pattern of Blaschko's lines because of the way in which epidermal cells grow out laterally from the neural crest.⁴ Melanoblasts in comparison grow out in single cell migration and proliferate antenatally in the skin, so they can give a variety of patterns including Blaschko's lines or phylloid and leaf-like or even checkerboard sometimes known as block type. Think of all the hyperpigmented variations that you have seen and you will get the idea. Blood vessels, fibroblasts and other mesodermal cells tend to take more direct routes into structures and hence nevi made up of these will usually be seen in embryonic segments or in actual dermatomes.

As a summary, if there are multiple organs involved then mosaicism occurred before organogenesis, and if the lesions are bilateral then mosaicism occurred before

lateralization. Mosaicism in the later stages of pregnancy, after the embryo has unfurled, is less likely to cause linear lesions than if it occurred early on when the embryo was still folded on itself. Mosaicism in the later stages of pregnancy from a somatic mutation is likely to cause oval or round patches while if the mutation is post natal you develop a tumour.

It is also useful to look at known inheritance patterns of various diseases and consider what effect mosaicism may have on them. These include some X-linked disorders that are often examples of X chromosome mosaicism and lyonization. There are other disorders that are autosomal lethal mutations, but they survive because of mosaicism. For example males get their X chromosome from their mothers. If the mother is heterozygous for a particular X-linked disorder the sons have a 50-50 chance of getting an abnormal X chromosome. If the condition is X-linked dominant the males usually die before birth e.g. incontinentia pigmenti and Goltz syndrome or focal dermal hypoplasia. If by some chance they survive then it is because of mosaicism, either somatic or half chromatid mutations.⁵

Chromosomal mosaicism occurs in hypomelanosis of Ito. This condition affects both males and females unlike incontinentia pigmenti. The chromosomal mosaicism can take the form of defects in both the chromosomal structure and number including both triploidy and translocations. The proteus syndrome is also interesting as an example of an autosomal lethal mutation that can only survive in a mosaic state. It occurs sporadically and has epidermal nevi

suggesting mosaicism although the exact nature of the mosaic disorder is not known.

The last concept to get over is what are known as type 1 mosaic disorders and type 2 mosaic disorders. In type 1 mosaic disorders you can have one segment involved with the rest of the skin being normal.⁶ In type 2 disorders the rest of the skin is abnormal but you have one normal segmental section and this is usually due to what is known as revertant mosaicism, where a gene defect that is affecting the rest of the body has reversed in this particular segment. This has been described as natural gene therapy. It is thought to explain some patients with conditions such as xeroderma pigmentosum who may have areas of normal skin in spite of their autosomal recessive trait. Other clinical examples include recessive epidermolysis bullosa simplex with an area of normal skin.

Twin spotting refers to the situation where two different mutations occur in the genetic material at the same site in paired chromosomes. When these split and recombine in mitosis two clones of cells may be formed that are now homozygous for each mutation and in close proximity to each other. An example is seen in adjacent segments of excessive or absent lesions in the skin in Darier's disease.

Occasionally knowledge of mosaicism is important in the field of genetic counseling. For example, if you have an early post-zygotic or post-fertilization mutation that involves both somatic and genetic cells, then the parent who suffered from this may have just a linear or localised variant of the disorder, but because the genetic cells or germ cells are involved, they may then have

a child with the generalized type of this disorder. An example of this is a localised epidermal nevus showing features of epidermolytic hyperkeratosis in a parent with the child subsequently having the generalized version of epidermolytic hyperkeratosis. This situation also may arise when called upon to give genetic advice on a child who is born with a rare genetic disease when both parents are apparently unaffected. You have to consider whether one of the parents may in fact have mosaicism in their germ cells even though they are not showing anything in the somatic cells because obviously, if they do, the risk of having a subsequent pregnancy affected by the same rare disease would be very much higher and some form of pre natal analysis of the embryo would be necessary.

Work in mosaicism is occurring all around the world. The mosaic nature of linear forms of common conditions such as psoriasis and eczema and vitiligo allows geneticists access to skin material which may give a greater insight into the genetic component of these disorders by comparing material from normal and abnormal areas in the same individual. The analysis of the human genome has given us the equivalent of the Rosetta tablet to explore these genetic disorders further and provide a greater understanding of the myriad forms of skin disease that we see.

References

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