

Genetic mosaicism: what Gregor Mendel didn't know.

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J Clin Invest. 1995;[95\(2\)](#):443-444. <https://doi.org/10.1172/JCI117682>.

Research Article

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The word "mosaic" was originally used as an adjective to describe any form of work or art produced by the joining together of many tiny pieces that differ in size and color (1). In that sense, virtually all multicellular organisms are mosaics of cells of different form and function. Normal developmentally determined mosaicism can involve permanent alterations of DNA in somatic cells such as the specialized cells of the immune system. In such specialized somatic cells, different rearrangements of germ line DNA for immunoglobulin and T cell receptor genes and the different mutations accompanying these rearrangements alter DNA and function. However, these alterations in individual cells cannot be transmitted to offspring since they occur only in differentiated somatic cells. Another form of normal mosaicism occurs in females. Virtually all mammalian females are mosaic with respect to their X chromosomes. Only one of the two X chromosomes carried by a female will be "active" in any given cell, with most of the other X rendered inactive by an as yet incompletely understood mechanism. Either the X chromosome inherited from the father (paternal X) or the X chromosome inherited from the mother (maternal X) is randomly inactivated during early embryogenesis. This inactivation pattern is passed on to all progeny of a single cell in somatic tissues. However germ line cells do not undergo X inactivation and this mosaicism is therefore not transmitted to offspring. As an additional form of normal mosaicism, all of us are quantitatively mosaic with respect to genes encoded in mitochondrial DNA. The mitochondrial genome is inherited only from the mother and is passed on to individual cells during cell division by a random process that potentially allows for distribution of unequal numbers to individual cells.

More recently, the term genetic mosaicism has been widely used to describe the presence, in a single individual, of two (or more) populations of cells that differ in their genetic constitution, or base sequence of DNA, from each other and from the DNA sequence present in the parents of the individual (2, 3). When the altered DNA sequence is ascertained in relation to inherited disease and can be transmitted to the offspring of the mosaic individual, the mosaicism is termed genetic. The most common cause of such genetic mosaicism is de novo mutations.

De novo mutations occur in cells throughout life and all of us carry cells that differ from the genetic endowment present in the fertilized egg. The time of occurrence, nature, and site of the de novo mutation will determine whether or not genetic mosaicism results. When de novo mutations occur postnatally and confer a growth advantage, they may contribute to development of malignancies, but they cannot be inherited. By contrast, postnatal de novo mutations that are detrimental to survival of the individual cell will disappear. Genetic mosaicism results when a mutation occurs early during development and is deleterious, so that sufficient somatic cells may be affected to result in disease in the individual (somatic mosaicism). If the mutation is present in cells of the germ line, the mutation may be transmitted to the offspring and result in a child completely affected for the trait caused by the mutation. Such germ line mosaicism,

depending on the developmental stage at which the mutation occurs, may or may not be associated with somatic mosaicism and may include all or only some of the germ cells. (A totally different mechanism for somatic mosaicism has been recently described, reversion of a transmitted mutation to normal [4]. We have additionally identified such an event [our unpublished observations].)

Somatic and germ line mosaicism were initially inferred on clinical grounds for a variety of diseases, including autosomal dominant and X-linked disorders, as presciently reviewed by Hall (3). Somatic mosaicism for inherited disease was initially definitively established for chromosomal disorders, such as Down's syndrome, and was often associated with milder phenotypes. More recently the availability of molecular techniques has documented somatic mosaicism for inherited disorders that do not follow classic patterns of Mendelian inheritance, such as mitochondrial inherited disorders and the increasing number of disorders due to expansion of triplet repeats. In diseases due to mutations in mitochondrial DNA, unequal distribution of normal and mutant mitochondrial DNA can occur (heteroplasmy) with resulting mosaicism. In disorders involving expansion of triplet repeats, the expansions may increase (and even decrease) during cell division, again resulting in mosaicism. Somatic and/or germ line mosaicism has also been documented molecularly with increasing frequency in disorders exhibiting classic Mendelian patterns of autosomal dominant and X-linked inheritance and much less frequently in autosomal recessive disorders (see references in 5 and 6).

If an inherited disease prevents reproduction (genetically lethal), de novo mutations should theoretically be present in all cases of such autosomal dominant disorders and in a third of cases of such X-linked diseases as X-linked severe combined immunodeficiency (SCID) (2). In X-linked disorders, these de novo mutations could have occurred in the maternal or grandparental germ line cells. The expected high frequency of de novo mutations for X-linked disorders also should lead to the occurrence of multiple different mutations in different patients. Because of this expected multiplicity of mutations, prenatal diagnosis and detection of females carrying the mutation have leaned on use of linkage to surrounding polymorphic markers. In this strategy, analysis of affected patients as well as members of preceding generations is used to define a series of normal polymorphic DNA markers surrounding or (preferably) within the mutated gene (haplotype). The presence of the mutant haplotype is then used for prenatal diagnosis as well as for determining if a family member carries the mutant gene. This widely used strategy does not require definition of the specific mutation present in the affected patient.

In this issue of *The Journal*, Puck et al. (7) report a family in which the grandmother had a son with SCID and two daughters who gave birth to affected males. Haplotype analysis indicated that a third daughter should also be a carrier of the mutant gene and at 50% risk for a male child with SCID. Fortunately for this family, Puck and co-workers applied the functional test they had previously validated for diagnosis of carrier females. The results indicated that the grandmother and the third daughter, diagnosed as a carrier by haplotype analysis, did not appear to be heterozygous for the mutation. Direct determination of the specific mutation segregating in this family confirmed that neither carried the

mutation in somatic cells. Therefore, the grandmother was a germ line mosaic for the mutation, transmitting the critical haplotype with the de novo mutation to three of her offspring and the same haplotype without the mutation to the fourth. As Puck et al. note, the frequency of de novo mutations and germ line mosaicism will undoubtedly be different for different genes on the X chromosome, depending on the underlying structure or "mutability" of the gene. The authors correctly indicate the need for direct determination of mutations for diagnosis. This currently formidable task for X-linked disorders may soon be feasible. Automated methodology for scanning of an entire gene, using an array of sequences on a single "chip" is currently under development. When available, this should allow for rapid detection of mutations in disorders where there is a multiplicity of different mutations in patients with the disease.

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