Review

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Somatic mosaicism: implications for disease and transmission genetics

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Nearly all of the genetic material among cells within an organism is identical. However, single-nucleotide variants (SNVs), small insertions/deletions (indels), copy-number variants (CNVs), and other structural variants (SVs) continually accumulate as cells divide during development. This process results in an organism composed of countless cells, each with its own unique personal genome. Thus, every human is undoubtedly mosaic. Mosaic mutations can go unnoticed, underlie genetic disease or normal human variation, and may be transmitted to the next generation as constitutional variants. We review the influence of the developmental timing of mutations, the mechanisms by which they arise, methods for detecting mosaic variants, and the risk of passing these mutations on to the next generation.

Introduction

A fundamental principle of biology is that the DNA blueprint of a multicellular organism is identical among cells within the organism. The term mosaicism describes a violation of this principle that arises when specific cells within a developing organism mutate to result in two or more cell populations with distinct genotypes. Mosaicism stands in contrast to chimerism, the phenomenon of an individual being composed of the products of two or more fertilization events. Multiple lines of evidence suggest that mutation during mitosis is a common event, with DNA changes going uncorrected on average every two cell divisions to even multiple mutations per division [1–3]. Given that as many as 10^{16} mitoses are required to generate an adult human composed of approximately 10^{14} cells [4], it is likely that cells within all of us harbor countless mutations that could potentially be causative of every human genetic disease. Nevertheless, almost none of these mutational events appear to affect organismal health. If detrimental to cellular function, mutant cells may be removed by apoptosis or immune surveillance. Otherwise, mutations may occur in a tissue where expression of the mutant gene is not relevant to function or disease, or mutant cells do not reach a proportion relevant to manifestation of a disease trait.

The exponential pace of cellular expansion during embryogenesis means that mutations occurring early during development have the most meaningful impact on the phenotype of an individual [5]. Mutations later in life, however, can transform cells with malignant potential, a process fundamental to cancer. This review focuses on non-oncologic phenotypes and processes. Conceptually, mosaicism can be categorized based on the distribution of mutant cells within the individual: somatic, germline, and gonosomal (see Glossary). Although molecular testing or observation of affected offspring can positively assign somatic, germline, or combined mosaicism status, definitively ruling out mosaicism in either the somatic or germ cell compartment is challenging with current technology. We explore below how the timing, mechanisms, and developmental histories of postzygotic mutations influence human health, disease, and potential risk of disease transmission.

Developmental timing of mutation

The precise timing during development when a mutation occurs strongly influences the distribution and phenotypic effects of mutant cells. In the most extreme case, a mutation can occur during the initial mitosis, resulting in approximately half of the cells in the individual harboring the new mutation (Figure 1A) – identical twins discordant

Glossary

Somatic mosaicism: genetic variation that is present in the genomes of cells that make up the body of the organism and do not contribute to gametes produced by the individual.
Gonadal mosaicism: genetic variation that is present in the genomes of cells that specifically contribute to the gametes.
Gonosomal mosaicism: genetic variation that is present in the genomes of both somatic cells and germline cells.
Constitutional variation: genetic variation that is present in the genome of every (or the vast majority of every) cell in an individual.
Postzygotic mutation: a mutation that occurs after the fertilization of the ovum by the sperm.
Simplex genetic disease: the first occurrence of a genetic disease in a family, which may be due to a *de novo* mutation, recessive inheritance in a small sibship, or an inherited dominant allele with reduced penetrance.

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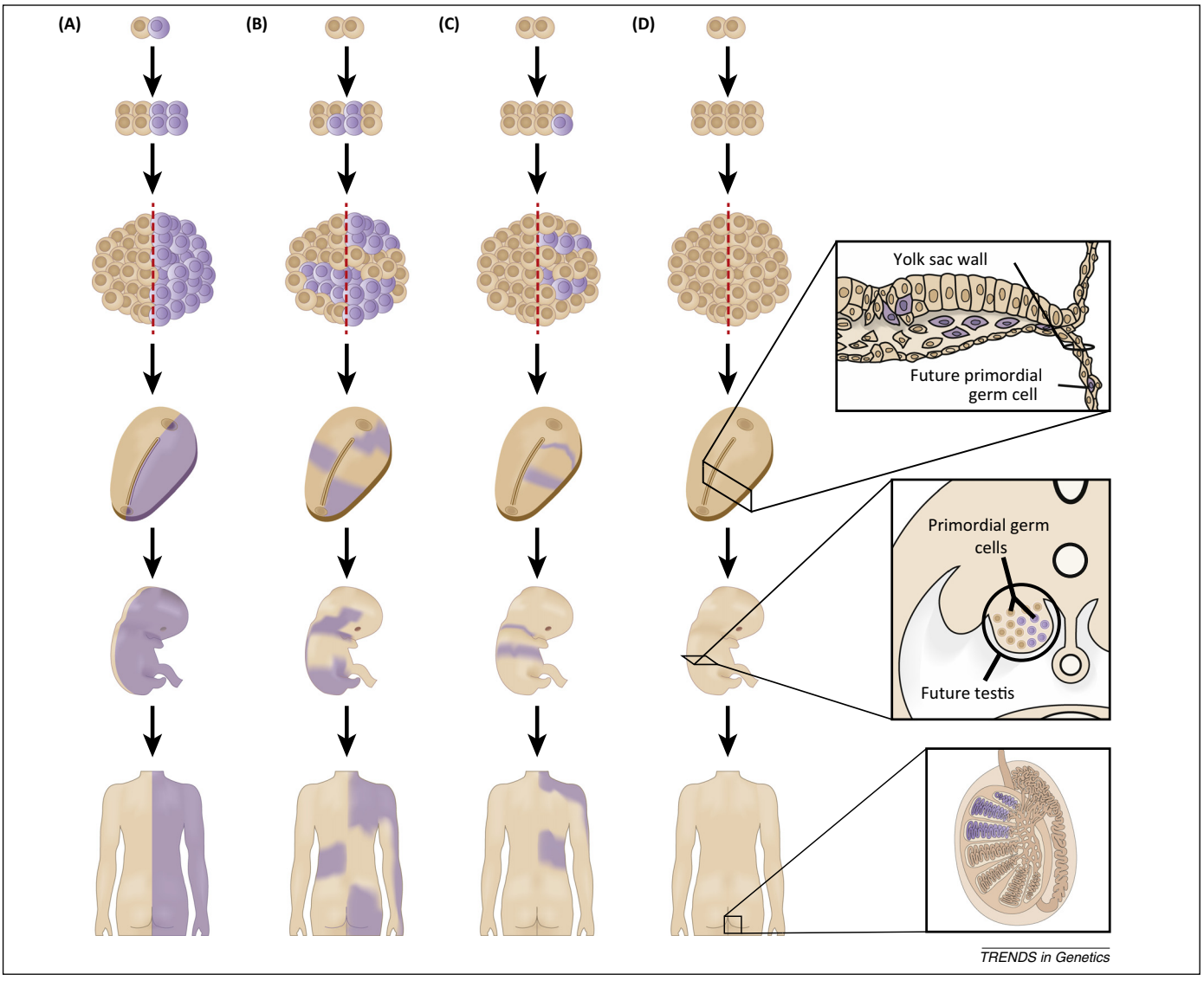

Figure 1. The timing of postzygotic mutation influences the distribution of mutant cells in the individual. **(A)** Mutations that occur during the first mitosis result in approximately half of the individual being affected. Individuals with CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) have been observed with this striking pattern (see Figure 2A). **(B)** Mutations that occur before left–right determination can affect both sides of the individual, including one or both gonads. **(C)** Mutations that arise after the determination of the two sides of the embryo can be confined to only one side of the individual. Only one gonad is likely to be affected. **(D)** Mutations that occur after differentiation of primordial germ cells (PGCs) will be absent from somatic tissues. Thus, molecular investigations to detect such gonadal mosaicism must involve direct observation of germ cells. For males, this process is relatively straight forward, but for females it involves invasive biopsy of potentially both ovaries.

for a dominant disorder caused by a new mutation might represent another manifestation of such a phenomenon [6]. Other signs of early embryologic mutational events may directly manifest in the observed phenotype. Individuals with congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome exhibit striking demarcation of affected and unaffected tissue along the midline (Figure 2A) [7]. The exact time of left–right separation in humans is unknown [8]; in mice it appears to occur around the eight cell stage [9]. If mutant cells arise before determination, and are present on both sides of the left–right axis, tissues on both sides of the individual can be affected, potentially including one or both gonads (Figure 1B). By contrast, mutations occurring after the fate of the left and right sides of the embryo have become determined result in cells and phenotypes that are less likely to cross the midline (Figure 1C). In such individuals, only one gonad, if either, is likely to harbor mutations.

The observation of many individuals with affected tissues on both left and right sides suggests that left–right determination in humans may occur later during development or that migrational boundaries are less definitive. An alternative hypothesis is that earlier mitoses are more prone to mutation. Studies suggest that such a heightened mutagenic process, or reduced repair and surveillance of genome instability, may occur during very early development [10,11]. Up to 70% of human embryos display CNV or whole chromosomal aneuploidies in at least one blastomere during the first week of embryogenesis [11]. Transcription is not fully activated in humans until the eight cell stage [12]; during this time, the embryo relies on maternally derived cytoplasmic and nuclear proteins while