

saccharide with chemical synthesis and then elaborated it with enzymes to provide 13 different complex *N*-glycan structures. They note that 85% of known *N*-glycans are asymmetrically branched and that, in principle, most of these can be accessed by this strategy.

To understand the roles of the core oligosaccharide and the branching structures of *N*-glycans in carbohydrate recognition, Wang *et al.* used a glycan array. They exposed the array to several glycan-binding proteins, including influenza virus hemagglutinins derived from different viral strains. The binding specificities obtained from the arrays containing only linear and symmetrically branched glycans were different than those obtained from arrays with asymmetrically branched glycans. There are mechanisms by which the sequence of each glycan

branch can influence protein recognition: Both branches can interact at an extended binding site, one branch could inhibit binding of another, or a symmetric branched glycan could engage in multivalent interactions (15).

The results reported by Wang *et al.* take us forward in fulfilling the need for well-defined glycans that match the complexity of those found in nature. Their methods provide the means to evaluate how glycan asymmetry influences the ability of glycan-binding proteins to distinguish between different yet related sequences. The study highlights the advantages of combining insights from chemistry and biology to access compounds that would otherwise be difficult to generate. Powerful tools needed to define the functions of specific glycans within the human glycome are now in our purview.

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## GENETICS

# Genome Mosaicism—One Human, Multiple Genomes

James R. Lupski

With recent advances in genome-wide assays, it is becoming increasingly apparent that a human individual is made up of a population of cells, each with its own “personal” genome. Thus, mosaicism is perhaps much more common within multicellular organisms than our limited genomic assays have detected thus far, and may represent the rule rather than the exception. To what extent does it play a role in normal development and disease?

Chromosomal mosaicism has been recognized clinically for decades, but the application of high-resolution genome-wide analysis tools, such as array comparative genomic hybridization and genomic single-nucleotide polymorphism (SNP) chips has allowed detection of events missed by karyotyping (1–3). Mosaicism for small intragenic copy number variants (CNVs) was detected in 10% of 30 molecularly diagnosed subjects (4), and extensive genomic CNVs have been found in clonal isolates of embryonic stem cells (5). In addition, varying levels of mosaicism have been reported in somatic human tissues, including the skin, brain, and blood, and in

induced pluripotent stem cells (6–10). Therefore, our understanding of the frequency and effects of mosaicism is increasing with the development of ever more sensitive methods for detecting genomic variation.

## The Origin of Mosaicism

Mosaicism can arise because of errors that occur during chromosome segregation or DNA replication, leading to chromosome aneuploidy, CNVs, genomic rearrangements, single-nucleotide variation, or repeat expansions and microsatellite instabilities. These mutational processes can occur at any stage of development; in stem cells, differentiating cells, and in terminally differentiated somatic cells.

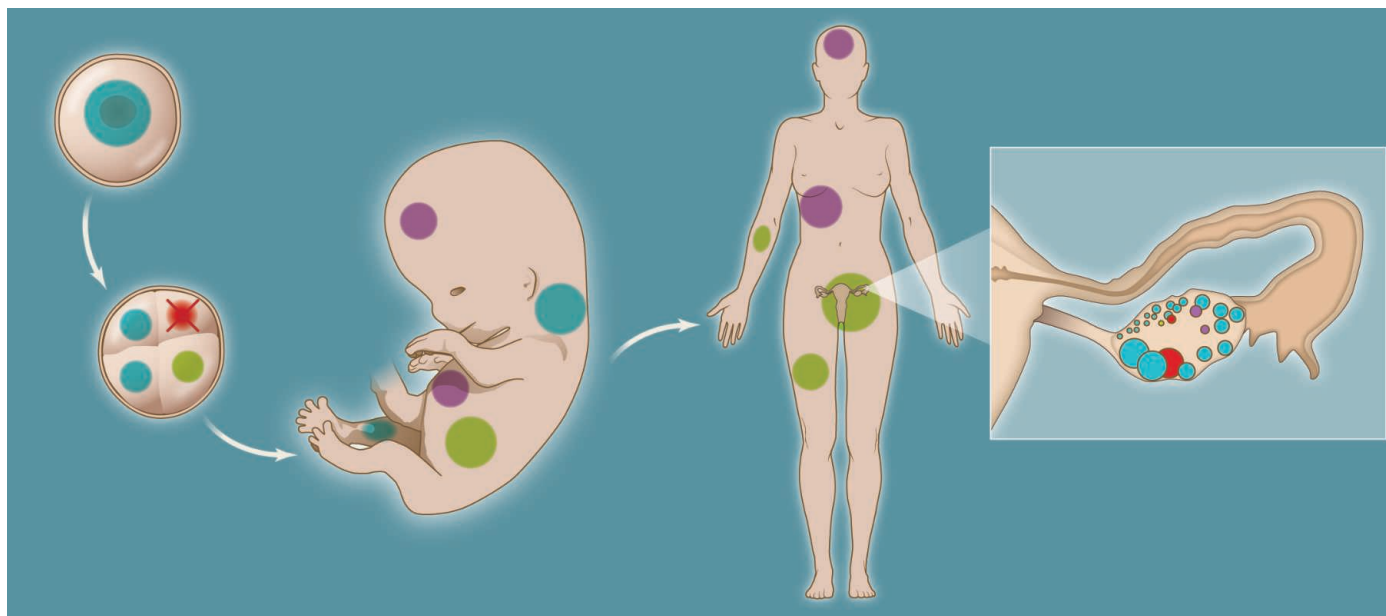
Both genomic architectural features (e.g., direct and inverted repeats) and DNA sequence characteristics (e.g., CpG dinucleotides) can increase genome instability and susceptibility to mutation. In addition, exogenous sources of DNA damage, such as tobacco smoke and other carcinogens, may lead to somatic mosaicism. Cumulative exposures to exogenous mutagens, as well as ongoing growth of the organism, cell proliferation and renewal, and tissue regeneration, result in accumulation of mutations with age. In addition, early studies suggested that

The cells in our body do not all contain identical genomes, which has implications for health and disease.

nonallelic homologous recombination–predicted inversions (i.e., structural variations) are mosaic and appear to accumulate as the individual ages (11). Somatic mosaicism can also be caused by L1 transposition during embryogenesis (12). Some unbalanced translocations appear to originate postzygotically, apparently arising *de novo* during embryogenesis in a process that is based on homologous interspersed transposable elements as substrates (13), and other postzygotic mutational events could potentially arise from recombination-restarted replication forks (14).

For both cellular and organismal populations, a balancing act must exist between mutation to generate variation and selection of the variants most fit for that given environment (see the figure). Development itself seems to be a process of strong selective pressure for human genomic integrity. Indeed, single-cell genomic analysis during early development reveals that chromosome instability is common in human cleavage-stage embryos (15), and abnormal chromosome complements can be found in about 70% of 14 normally developing human embryos examined (16); whereas such extensive genomic abnormalities are rare in live-born individuals. Perhaps mutation is tolerated to a

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**Acquiring mosaicism.** Human development from a single fertilized cell to a multicellular organism requires many cell divisions and the genetic material to be replicated many times. Populations of cells (blue) can accumulate mutations

at any stage in the life cycle (green, purple, and red). Some impair cellular fitness, and are consequently selected against (red cross); others survive and contribute to tissue mosaicism, which may serve physiological functions.

greater extent, or selection is less restrictive, in a cell-autonomous environment than in the whole organism.

#### Possible Biological Functions

In terms of pathological functions, somatic mosaicism of terminally differentiated cells has long been known to cause cancer. Recent work shows that somatic mosaicism of nervous system tissues underlies a host of neurodevelopmental and perhaps neuropsychiatric diseases (17). However, the extent of somatic mosaicism that is now being reported in a variety of healthy tissues and cell types suggests that it also has physiological functions. The most well-characterized function for genome mosaicism is in the immune system, in which intra-individual lymphocyte genetic diversity is generated by mainly recombination and somatic hypermutation to combat a wide variety of pathogens and antigens. It has also been hypothesized that the complexity and diversity of neuronal cell types in the human brain arose by somatic retrotransposition (7, 8), and that mosaicism might even play a role in normal brain function. However, more work is needed to determine whether somatic mosaicism has direct biological functions in specific tissues.

#### Clinical Implications

Mosaicism of both somatic tissues and germ cells in humans has several clinical implications. Recurrence risk for unaffected parents who have an affected child and are contemplating a pregnancy may relate to the

frequency of new mutations at a given gene or locus, the severity of the phenotype conferred by mosaicism, the type of mutational mechanism, or the sex and age of the mosaic parent. Mosaicism and risk for recurrence in offspring may also relate to the time in embryogenesis at which the de novo mutational event occurred. If the parent is germline mosaic, he or she is at risk for a recurrence of another child with the disease.

Mosaicism is also important for disease mechanism. For example, somatic activating mutations in the protein kinase AKT1 are associated with Proteus syndrome, whereas mosaicism for postzygotic mutations in genes for three core components of the phosphatidylinositol 3-kinase (PI3K)–AKT signaling pathway that enhance signaling can cause a spectrum of related megalencephaly syndromes (17).

From a diagnostics standpoint, it is important to realize that genome analyses reflect the average genome of the cells one examines. Thus, for chorionic villus sampling, an abnormality observed may represent confined placental mosaicism. When performing karyotype analysis from a blood sample, only cells stimulated to grow are assayed for chromosomes, whereas total DNA isolated from white blood cells comes from more cell types and thus may detect mosaicism (1, 2). However, none of these approaches informs on the presence of mosaicism in the brain or other tissues and organs. Skin biopsies are more representative of germline genomic constituents than blood cells, particularly with older

individuals, likely reflecting the more rapid cell turnover, greater selective evolutionary forces, and multitude of cellular constituents of blood. Eventually, genome analysis of all surgically excised abnormal tissue (tonsils, an appendix, a defective heart valve, or abnormal skeletal muscle), not just cancer, might be considered germane for genome analysis to detect mosaicism—or perhaps even the presence of a foreign viral or microbial genome. Such studies may prove informative in the clinic.

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