Review

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Mosaicism and uniparental disomy in prenatal diagnosis

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Chromosomal mosaicism is the presence of numerous cell lines with different chromosomal complements in the same individual. Uniparental disomy (UPD) is the inheritance of two homologous chromosomes from the same parent. These genetic anomalies arise from errors in meiosis and/or mitosis and can occur independently or in combination. Due to the formation mechanisms of UPD, low-level or undetected mosaicisms are assumed for a significant number of UPD cases. The pre- and postnatal clinical consequences of mosaicism for chromosomal aberrations and/or UPD depend on the gene content of the involved chromosome. In prenatal evaluation of chromosomal mosaicism and UPD, genetic counseling should be offered before any laboratory testing.

Chromosomal mosaicism in human pregnancy

With the advent of individualized whole-genome sequencing in the past decade, it has become obvious that each individual has its own genetic constitution comprising thousands of SNPs and copy number variations, most of which are apathogenic. These variants are often inherited, but variations can also arise *de novo* during parental meiosis or during development. In the case of *de novo* mutations, different cell populations within the same individual can develop, leading to the presence of numerous cell lines with different chromosomal complements in the same individual. This is referred to as a 'mosaic' constitution (Figure 1). While there are limited data on the role of mosaicism of single-gene mutations, chromosomal mosaicism, as the presence of multiple cell lines with different chromosomal complements in the same individual, is now a well-known observation in genetic testing. Mosaic aneuploidy (see Glossary) is found in 1–2% of prenatal diagnoses performed by chorionic villus sampling (CVS) [1] and in around 0.2% of all amniocenteses [2] (Box 1).

While complete trisomy is viable for certain chromosomes only (chromosomes 13, 18, and 21 and the gonosomes), zygotes carrying other trisomies or monosomies

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Glossary

Amniocentesis: an invasive prenatal genetic testing method comprising sampling of the amniotic fluid. It is usually performed between 16 and 20 weeks of pregnancy.
Aneuploidy: aberrant chromosomal constitution in which the number of chromosomes differs from wild type.
Chorionic villous sampling (CVS): an invasive prenatal genetic testing method comprising sampling of the chorionic villi (placental tissue). CVS is usually performed at 10 –12 weeks of gestation.
Confined placental mosaicism (CPM): aneuploidy mosaicism restricted to the placenta.
Deletion: aberration in which part of a chromosome or DNA sequence is missing.
Differentially methylated region (DMR): a genomic region with differential methylation status between different tissues, with a function in epigenetic regulation of gene expression.
DNA methylation: a molecular modification of DNA where a methyl group is added to cytosine residues.
Duplication: an aberration in which part of a chromosome or DNA sequence is duplicated.
Epigenetic modifications/epimutations: molecular alterations not causing changes in the DNA sequence itself but affecting gene expression by aberrant silencing or activation (e.g., by aberrant DNA methylation).
Imprinted genes: genes that are expressed only from one parental allele, either the maternal or the paternal.
Imprinting control region (ICR): a chromosomal region that regulates the expression or silencing of imprinted genes.
Imprinting disorder (ID): a group of (currently eight) congenital disorders caused by molecular alterations of imprinted genes (or chromosomal regions). Imprinted genes are genes that are expressed in a parent-of-origin-specific manner.
Isochromosome: a chromosome that has lost one of its arms and replaced it with an exact copy of the other arm.
Microsatellite (short tandem repeat): repeating DNA sequences of 2–5 bp. They are stably inherited from parents and can therefore be used as markers for linkage or kinship studies.
Molecular karyotyping: digital analysis of data obtained from the analysis of short DNA sequences from loci all over the genome. It detects genomic copy number variations at a higher resolution than conventional karyotyping.
Multilocus methylation defect (MLMD): where more than one imprinted locus shows aberrant methylation patterns.
Parental conflict hypothesis: states that the inequality of imprinting patterns between parental genomes is a result of the differing biological interests of the parents.
Pseudomosaicism: the finding of chromosomal abnormalities in 2% or fewer of the cells of an organism.
Small supernumerary marker chromosomes (sSMCs): small, additional, structurally abnormal chromosomes that cannot be identified or characterized by conventional cytogenetics. In the cytogenetic nomenclature, they are abbreviated as +mar.
Translocations: rearrangement of parts of between chromosomes. When the acrocentric chromosomes 13, 14, 15, 21, or 22 are involved, this rearrangement is called a Robertsonian translocation.
Trisomy: a numerical chromosomal aberration with three instances of a particular chromosome instead of the normal two.
Uniparental disomy (UPD): the unique inheritance of both chromosomes of the same pair from only one parent, not from both parents.
Uniparental heterodisomy (UPhD): the presence of both parental homologs of a pair of chromosomes in a 46,XN karyotype.
Uniparental isodisomy (UPiD): the presence of two copies of one parental homolog of a pair of chromosomes in a 46,XN karyotype.

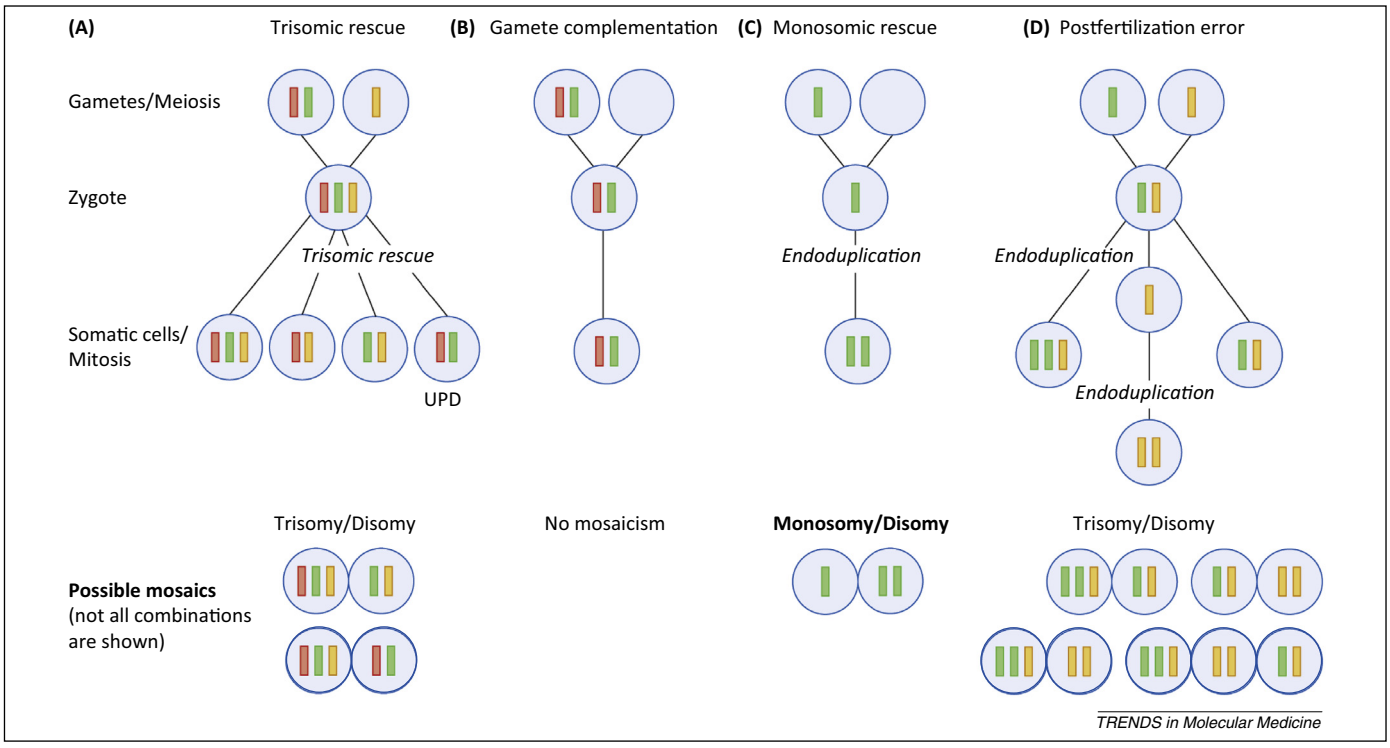

Figure 1. The four uniparental disomy (UPD) formation mechanisms and possible mosaic constitutions. Disomy/monosomy mosaicism is extremely rare because of the lethality of monosomy. The mechanism of formation of segmental UPD is not illustrated.

may survive if the aneuploidy is corrected and a 'normal' diploid karyotype is restored (Box 2 and Figure 1). The proportion of normal to monosomic/trisomic cell lines in different tissues can vary remarkably and is known as mosaicism. The lack of mosaicism in one tissue does not exclude its absence in another tissue. Prenatally, this variable mosaic distribution complicates the prediction of pregnancy outcome as the mosaicism might be confined to the placenta or to the fetus, or it might affect both [3] (Box 1). One example of a viable discrepant mosaic distribution is Pallister–Killian syndrome, a rare congenital disorder caused by a supernumerary isochromosome of the short arm of chromosome 12 resulting in functional tetrasomy 12p. This isochromosome 12p is commonly detected in fibroblasts but is usually not present in lymphocytes [4].

It has been suggested that undetected mosaicism could be a frequent cause of phenotypic abnormality even when a fetus or child has a normal karyotype in the tissue analyzed [5,6]. Furthermore, chromosomal mosaicism might also be associated with the formation of UPD.

Box 1. CVS, amniocentesis, and mosaicism

The distribution of chromosomally normal and abnormal cell lines in the fetus and its placenta depends on the time and the tissue of the mitotic error. Where trisomic rescue has occurred at an early embryonic stage and affects a cell giving rise to the inner cell mass and some extrafetal tissues, the embryo might show 46,XN and the placenta a mosaic trisomy 47,XN,+?/46,XN (CPM) [2]. Alternatively, CPM for a non-mosaic trisomic fetus 47,XN,+? and a mosaic placenta 47,XN,+?/46,XN could also be observed, while a third possibility is fetal mosaicism 47,XN,+?/46,XN and a placenta with a normal chromosomal complement 46,XN. Mosaicism can also be distributed in both the placenta and the embryo. If rescue occurs later in pregnancy, the placenta might be entirely trisomic, with a mosaic aberrant or non-mosaic constitution of the fetus.

For the two invasive prenatal testing procedures, CVS and amniocentesis, the identification of a mixture of chromosomally normal and abnormal cells is a great challenge and requires careful work-up, including the analysis of a huge number of cells in different parallel cell cultures [ACC Professional Guidelines in Clinical Cytogenetics (2007) (http://www.cytogenetics.org.uk)]. To standardize the interpretation of prenatal mosaicism, different levels of *in vitro* mosaicism have been defined [2,63], ranging from level I (a single aberrant cell, probably a cultural artifact, called 'pseudo-mosaicism') to level II (two or more cells with the same aberration in a single flask) and level III (two or more aberrant cells in independent cultures, reflecting true mosaicism). However, this classification is artificial and conflicting results have been reported (e.g., [58]).

The phenotypic outcome of prenatal mosaicism is influenced by the tissue distribution of the affected cells and the involved chromosome or chromosomal region. Its prediction is mainly based on published cases, but these reports show that a reliable prognosis in an individual is almost impossible [2].

UPD: definition, frequency, and clinical complications

The concept of UPD was first postulated by Eric Engel [7] and describes the exceptional inheritance of both homologs of a pair of chromosomes from only one parent (Figure 1 and Box 2). Two types of UPD can be differentiated: uniparental heterodisomy (UPhD), where two different alleles of the same parents are transmitted; and uniparental isodisomy (UPiD), where two identical copies of one allele of the contributing parent can be detected. In many cases, both types can be observed in the same carrier, caused by meiotic recombination (Box 2). Furthermore, UPD can affect only part of a chromosome; this situation is called segmental UPD and often occurs in Beckwith–Wiedemann syndrome (BWS) (Table 1).

The occurrence of human disease resulting from UPD was first demonstrated by Spence *et al.* [8], who found