UNIPARENTAL DISOMY INFORMATION

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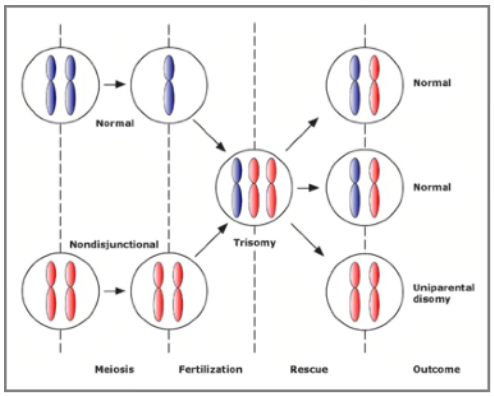

Each healthy person has two homologous chromosomes: one inherited from the mother and another from the father. Uniparental disomy (UPD) is a condition when both chromosomes of the same pair are inherited from only one parent. Theoretically the possibility of such a situation was predicted by Eric Engel in 1980[1], but confirmation of this phenomenon became possible only after the introduction of different methods of molecular cytogenetics. The number of reported observations of UPD is growing rapidly; the recent review by Liehr[2] includes ~ 5000 reported cases (including the so-called partial UPD).

A very basic question: how does it occur? It has been shown that a cell at the very early stages of development has a unique opportunity to auto-correct existing chromosomal defects. If the zygote (or very early embryo) has an additional chromosome the cell can try restoring a normal condition by expelling the extra chromosome. Assume that an egg-cell has for example two chromosomes 16 (instead of normally one). The fertilization of such an egg-cell by a normal sperm will lead to a zygote with three chromosomes 16 (two from the egg-cell and one from the sperm). Expulsion of the extra chromosome occurs randomly: if one maternal chromosome 16 is expelled it will restore a normal diploid karyotype. But if the paternal chromosome 16 is expelled, the restored cell will remain with two maternal chromosomes 16. Restoration of the previously trisomic cell is the main mechanism for the formation of UPD. Of course, it is not possible to diagnose UPD using “standard” cytogenetics, because under the microscope each cell will look completely

normal. Molecular methods however are able to show that both homologous chromosomes (in our case both chromosomes 16) are maternal. Therefore, the primary event leading to the origin of UPD is a non-disjunction of chromosomes upon formation of the egg-cell or sperm-cell.

Typically, each person has two different homologous chromosomes, one inherited from each parent. Chromosomes 16 (the number 16 is used here only as an example, the same is true for any autosome) in each person may be marked as 16^{F} [inherited from the mother] and 16^{P} [inherited from the father]. Each maternal chromosome 16 may be inherited from her mother: $16^{F(F)}$ and from her father $16^{F(P)}$. For the man it will be $16^{P(F)}$ and $16^{P(P)}$. Depending upon the stage of cell division non-disjunction can lead to the occurrence of the egg-cell with two different chromosomes 16 [$16^{F(F)}$, $16^{F(P)}$] or with two identical chromosomes 16 [$16^{F(F)}$, $16^{F(F)}$] or [$16^{F(P)}$, $16^{F(P)}$]. Basically the same mechanism occurs upon the formation of the sperm-cells. If after the expulsion of the paternal chromosome 16 we see a person with two <u>different</u> maternal chromosomes 16 this condition is called heterodisomy. If however both chromosomes 16 are identical it is called isodisomy.

Theoretically it is possible that UPD can occur as a restoration of the primary monosomic cell, but the percentage of such cases in the general UPD pool is hardly significant. All UPD is such cases are isodisomic.

UPD occurs for all chromosomes, but chromosomes 15 and 16 are preferentially involved[2,3]. Maternal UPD occurs 2-3 times more frequently than paternal[2,3]. Of course, the diagnosis of isodisomy is much easier, because this form of UPD will is evident upon each molecular cytogenetic examination of the person. A conclusion about heterodisomy requires a special cytogenetic examination of the parents (or at least one of them).

The basic question is: what are the clinical consequences of UPD? In the vast majority of cases UPD remains unrecognized and persons with two homologous chromosomes inherited from one parent are absolutely healthy. However, clinical problems may occur in several situations:

1) The affected chromosome may carry a gene causing an autosomal-recessive condition. If such a gene has a normal copy on the other homologues chromosome it will not cause any problems. But if the mutant gene is found on both copies of the chromosome (as it may happen in isodisomy) it may lead to a genetic disorder. Most currently reported cases of UPD were found upon examinations of patients with unexpectedly occurring recessive conditions.

2) Sometimes “restoration” of the normal chromosome number occurs in the embryo, and it is possible that part of cells may still have a trisomy (which caused the formation of UPD). In such cases some additional effects may be explained by the residual existence of the trisomic clone.

3) Some chromosomes (but not all) contain segments which are differently expressed on maternal and paternal chromosomes. This phenomenon has a name of genetic imprinting. The clinical consequences of silencing of maternal or paternal imprinted areas are strongly different: for example maternal UPD for the short arm of chromosome 11 leads to Silver-Russell syndrome (a form of growth delay), whereas paternal UPD for the same segment causes Beckwith-Wiedemann syndrome (a form of overgrowth).

Currently known areas which may be affected by imprinting include 6q24, 11p15, 14q32 and 15q11q13.

REFERENCES

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[2] Liehr T: Uniparental disomy is a chromosomic disorder in the first place. Molec Cytogenetics 2022, v. 15:5.

[3] Benn P: Uniparental disomy: origin, frequency, and clinical significance. Prenatal Diagn. 2021, v. 41, 564-572.

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